(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 August 2003 (14.08.2003)

PCT

(10) International Publication Number
WO 03/066597 A2

(51) International Patent Classification[7]: C07D 215/08, 217/06, 401/06, 223/16, 217/14, 221/10, 401/04, 295/12, 295/20, A61K 31/47, 31/4709, 31/472, 31/4725, 31/495, 31/496, A61P 3/04, 3/10

(21) International Application Number: PCT/US03/01078

(22) International Filing Date: 3 February 2003 (03.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/353,188	4 February 2002 (04.02.2002)	US
10/351,574	27 January 2003 (27.01.2003)	US

(71) Applicant *(for all designated States except US)*: CHIRON CORPORATION [US/US]; 4560 Horton Street, Emeryville, CA 94608 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BOYCE, Rustum [IN/US]; 1818 Broadway #206, San Francisco, CA 94109 (US). CHU, Daniel [US/US]; 3767 Benton Street, Santa Clara, CA 95051 (US).

(74) Agents: COLLIER, Steven, W. et al.; Chiron Corporation, Intellectual Property R338, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/066597 A2

(54) Title: GUANIDINO COMPOUNDS

(57) Abstract: A variety of small, guanidino group-containing molecules capable of acting as MC4-R agonists are provided. The compounds have various structures provided herein. The compounds are useful in treating MC4-R mediated diseases and may be formulated into pharmaceutical formulations and compositions.

GUANIDINO COMPOUNDS

Field of the Invention

This invention relates to melanocortin-4 receptor (MC4-R) agonists and methods of their preparation. The invention also relates to methods of treating melanocortin-4 receptor-mediated diseases, such as obesity or diabetes, by activating the melanocortin-4 receptor with compounds provided herein.

Background of the Invention

Melanocortins are peptide products resulting from post-translational processing of pro-opiomelanocortin and are known to have a broad array of physiological activities. The natural melanocortins include the different types of melanocyte stimulating hormone (α-MSH, β-MSH, γ-MSH) and ACTH. Of these, α-MSH and ACTH are considered to be the main endogenous melanocortins.

The melanocortins mediate their effects through melanocortin receptors (MC-Rs), a subfamily of G-protein coupled receptors. There are at least five different receptor subtypes (MC1-R to MC5-R). MC1-R mediates pigmentation of the hair and skin. MC2-R mediates the effects of ACTH on steroidogenesis in the adrenal gland. MC3-R and MC4-R are predominantly expressed in the brain. MC5-R is considered to have a role in the exocrine gland system.

The melanocortin-4 receptor (MC4-R) is a seven-transmembrane receptor. MC4-R may participate in modulating the flow of visual and sensory information, coordinate aspects of somatomotor control, and/or participate in the modulation of autonomic outflow to the heart. K. G. Mountjoy *et al.*, *Science, 257*:1248-125 (1992). Significantly, inactivation of this receptor by gene targeting has resulted in mice that develop a maturity onset obesity syndrome associated with hyperphagia, hyperinsulinemia, and

hyperglycemia. D. Husznar *et al.*, *Cell, 88(1)*: 131-41 (1997). MC4-R has also been implicated in other disease states including erectile disorders, cardiovascular disorders, neuronal injuries or disorders, inflammation, fever, cognitive disorders, and sexual behavior disorders. M. E. Hadley and C. Haskell-Luevano, The proopiomelanocortin system, *Ann. N. Y. Acad. Sci.*, *885*:1 (1999).

Furthermore, observations in connection with endogenous MCx-R antagonists indicate that MC4-R is implicated in endogenous energy regulation. For example, an agouti protein is normally expressed in the skin and is an antagonist of the cutaneous MC receptor involved in pigmentation, MC1-R. M. M. Ollmann *et al.*, *Science, 278*:135-138 (1997). However, overexpression of agouti protein in mice leads to a yellow coat color due to antagonism of MC1-R and increased food intake and body weight due to antagonism of MC4-R. L. L. Kiefer *et al., Biochemistry, 36*: 2084-2090 (1997); D. S. Lu *et al., Nature,* 371:799-802 (1994). Agouti related protein (AGRP), an agouti protein homologue, antagonizes MC4-R but not MC1-R. T. M. Fong *et al., Biochem. Biophys. Res. Commun. 237*:629-631 (1997). Administration of AGRP in mice increases food intake and causes obesity but does not alter pigmentation. M. Rossi *et al., Endocrinology, 139*:4428-4431 (1998). Together, this research indicates that MC4-R participates in energy regulation, and therefore, identifies this receptor as a target for a rational drug design for the treatment of obesity.

In connection with MC4-R and its uncovered role in the etiology of obesity and food intake, the prior art includes reports of compounds and compositions that act as agonists or antagonists of MC4-R. As examples, U.S. Patent No. 6,060,589 describes polypeptides that are capable of modulating signaling activity of melanocortin receptors. Also, U.S. Patent Nos. 6,054,556 and 5,731,408 describe families of agonists and antagonists for MC4-R receptors that are lactam heptapeptides having a cyclic structure. WO 01/10842 discloses MC4-R binding compounds having a multitude of structures and methods of using such compounds to treat MC4-R associated

disorders. Some of the compounds described include amidino- and guanidino-containing arenes and heteroarenes.

Various other classes of compounds have been disclosed as having MC4-R agonist activity. For example, WO 01/70708 and WO 00/74679 disclose MC4-R agonists that are piperidine compounds and derivatives, while WO 01/70337 and WO 99/64002 disclose MC-R agonists that are spiropiperidine derivatives. Other known melanocortin receptor agonists include aromatic amine compounds containing amino acid residues, particularly tryptophan residues, as disclosed in WO 01/55106. Similar agonists are disclosed in WO 01/055107 which comprise aromatic amine compounds containing tertiary amide or tertiary amine groups. Finally, WO 01/055109 discloses melanocortin receptor agonists comprising aromatic amines which are generally bisamides separated by a nitrogen-containing alkyl linker.

Guanidine-containing compounds having a variety of biological activities are also known in the prior art. For example, U.S. patent No. 4,732,916 issued to Satoh *et al.* discloses guanidine compounds useful as antiulcer agents; U.S. Patent No. 4,874,864, U.S. Patent No. 4,949,891, and U.S. Patent No. 4,948,901 issued to Schnur *et al.* and EP 0343 894 disclose guanidino compounds useful as protease inhibitors and as anti-plasmin and anti-thrombin agents; and U.S. Patent No. 5,352,704 issued to Okuyama *et al.* discloses a guanidino compound useful as an antiviral agent. Guanidine-containing compounds are also disclosed in other references. For example, U.S. Patent No. 6,030,985 issued to Gentile *et al.* discloses guanidine compounds useful for treating and preventing conditions in which inhibition of nitric oxide synthetase is beneficial such as stroke, schizophrenia, anxiety, and pain. U.S. Patent No. 5,952,381 issued to Chen *et al.* discloses certain guanidine compounds for use in selectively inhibiting or antagonizing $\alpha_v\beta_3$ integrins.

Various 5-, 6-, and 7- membered fully saturated 1-azacarbocyclic-2-ylidene derivatives of guanidine are disclosed as having anti-secretory and hypoglycemic activities by U.S. Patent No. 4,211,867 issued to Rasmussen. Such compounds are also taught as useful for the treatment of cardiovascular disease. Other guanidine derivatives are disclosed by U.S. Patent No. 5,885,985 issued to Macdonald *et al.* as useful in therapy to treat inflammation.

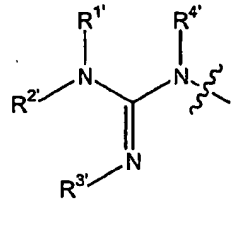
Nevertheless, there remains a need for potent and specific agonists of MC4-R that are low molecular weight small molecules. Methods of treating a melanocortin-4 receptor mediated disease, such as obesity, with such non-peptide drugs, are also particularly desirable.

Summary of the Invention

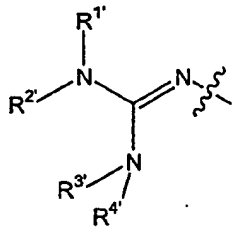
The instant invention provides potent and specific agonists of MC4-R that are low molecular weight small molecules. Thus, there has been provided, in accordance with one aspect of the invention, compounds of formula A^1-A^2-A^3-A^4:

wherein

A^1 is a group of formula IIA or IIB;



IIA



IIB

$R^{1'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

$R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups; or

$R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl or heteroaryl group;

$R^{3'}$ is selected from the group consisting of substituted and unsubstituted aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

$R^{4'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, and heteroarylalkyl groups;

A^2 is selected from the group consisting of substituted and unsubstituted aryl groups and substituted and unsubstituted heteroaryl groups;

A^3 is a covalent bond such that A^2 is directly bonded to A^4, or A^3 is a linking group selected from the group consisting of O, S, $-NR^a-$, $-C(=O)-$, $-C(=O)O-$, $-NR^aC(=O)-$, $-SO_2NR^a-$, $-C(=S)-$, $-C(=O)S-$, $-P(=O)R^b-$, $-SO_2-$, and $-S(=O)-$, wherein if A^3 is a linking group, then it is bonded to A^2 and A^4 in a configuration selected from the group consisting of A^2-O-A^4, A^2-S-A^4, A^2-NR^a-A^4, A^2-C(=O)-A^4, A^2-C(=O)O-A^4, A^4-C(=O)O-A^2, A^2-NR^aC(=O)-A^4, A^4-NR^aC(=O)-A^2, A^2-SO_2NR^a-A^4, A^4-SO_2NR^a-A^2, A^2-C(=S)-A^4, A^2-(C=O)S-A^4, A^4-(C=O)S-A^2, A^2-(P=O)R^b-A^4, A^2-SO_2-A^4, and A^2-S(=O)-A^4 provided that if A^3 is a linking group with the configuration A^4-NR^aC(=O)-A^2, then A^2 is not a

substituted or unsubstituted phenyl group and is not a substituted or unsubstituted 6-membered N-containing heteroaryl group;

A^4 is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups;

R^a is selected from the group consisting of H, and substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups; and

R^b is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups.

Compounds provided by the invention further include prodrugs of the compound of A^1-A^2-A^3-A^4, pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, hydrates thereof, hydrides thereof, or solvates thereof.

The invention provides further compounds of formula A^1-A^2-A^3-A^4 in which A^2 is selected from the group consisting of substituted and unsubstituted phenyl groups and substituted and unsubstituted pyridyl groups.

The invention further provides compounds in which A^3 is a linking group bonded to A^2 and A^4 in a configuration selected from the group consisting of A^2-NR^a-A^4, A^2-C(=O)-A^4, A^2-C(=O)O-A^4, A^4-C(=O)O-A^2, A^2-NHC(=O)-A^4, A^2-SO_2NH-A^4, and A^2-SO_2-A^4.

The invention provides further compounds of formula A^1-A^2-A^3-A^4 in which $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cycloalkyl, polycyclic cycloalkyl, alkenyl, alkyl, and aryl groups. In other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{3'}$ is

selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-alkylcyclohexyl, 2,2-dialkylcyclohexyl, 2,3-dialkylcyclohexyl, 2,4-dialkylcyclohexyl, 2,5-dialkylcyclohexyl, 2,6-dialkylcyclohexyl, 3,4-dialkylcyclohexyl, 3-alkylcyclohexyl, 4-alkylcyclohexyl, 3,3,5-trialkylcyclohexyl, cyclohexylmethyl, 2-aminocyclohexyl, 3-aminocyclohexyl, 4-aminocyclohexyl, 2,3-diaminocyclohexyl, 2,4-diaminocyclohexyl, 3,4-diaminocyclohexyl, 2,5-diaminocyclohexyl, 2,6-diaminocyclohexyl, 2,2-diaminocyclohexyl, 2-alkoxycyclohexyl, 3-alkoxycyclohexyl, 4-alkoxycyclohexyl, 2,3-dialkoxycyclohexyl, 2,4-dialkoxycyclohexyl, 3,4-dialkoxycyclohexyl, 2,5-dialkoxycyclohexyl, 2,6-dialkoxycyclohexyl, 2,2-dialkoxycyclohexyl, 2-alkylthiocyclohexyl, 3-alkylthiocyclohexyl, 4-alkylthiocyclohexyl, 2,3-dialkylthiocyclohexyl, 2,4-dialkylthiocyclohexyl, 3,4-dialkylthiocyclohexyl, 2,5-dialkylthiocyclohexyl, 2,6-dialkylthiocyclohexyl, 2,2-dialkylthiocyclohexyl, cyclopentyl, cycloheptyl, cyclohexenyl, isopropyl, n-butyl, cyclooctyl, 2-arylcyclohexyl, 2-phenylcyclohexyl, 2-arylalkylcyclohexyl, 2-benzylcyclohexyl, 4-phenylcyclohexyl, adamantyl, isocamphenyl, carenyl, 7,7-dialkylnorbornyl, bornyl, norbornyl, and decalinyl groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-methylcyclohexyl, 2,2-dimethylcyclohexyl, 2,3-dimethylcyclohexyl, 2,4-dimethylcyclohexyl, 2,5-dimethylcyclohexyl, 2,6-dimethylcyclohexyl, 3,4-dimethylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, cyclohexenyl, 3,3,5-trimethylcyclohexyl, 4-*t*-butylcyclohexyl, cyclohexylmethyl, isopinocampheyl, 7,7-dimethylnorbornyl, 4-isopropylcyclohexyl, and 3-methylcycloheptyl groups.

The invention provides further compounds of formula A^1-A^2-A^3-A^4 in which $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and

thiophene groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups.

In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl group. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted saturated heterocyclyl group comprising at least one heteroatom selected from the group consisting of O, S, and N, in addition to the nitrogen atom to which $R^{1'}$ and $R^{2'}$ are bound. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted piperazino, morpholino, pyrrolidino, piperidino, homopiperazino, or azepino group. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazino group optionally substituted by one or two methyl groups.

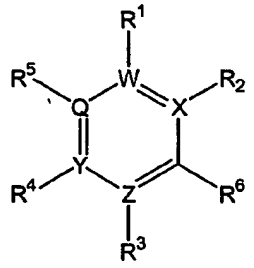
The invention provides further compounds of formula A^1-A^2-A^3-A^4 in which R^a is H.

The invention provides further compounds of formula A^1-A^2-A^3-A^4 in which A^3 is a covalent bond so that A^2 is directly bonded to A^4.

The invention provides further compounds of formula A^1-A^2-A^3-A^4 in which A^4 is a 2,4-disubstituted phenylethyl group or an

indolylethyl group. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, A^4 is selected from the group consisting of 2,4-dihalophenylethyl, and 2,4-dialkylphenylethyl groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, A^4 is selected from the group consisting of phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 2-fluoro-4-bromophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-fluorophenylethyl, 2,4-difluorophenylethyl, 2,4-dimethylphenylethyl, or 2,4-dimethoxyphenylethyl groups.

In accordance with another aspect of the invention, there has been provided, a compound of formula I:



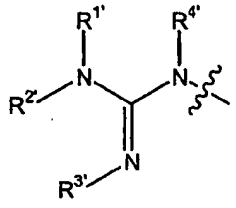
I

wherein

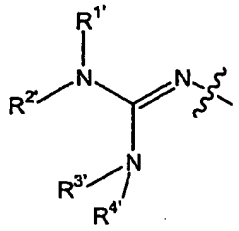
Q, W, X, Y, and Z are independently selected from the group consisting of carbon atoms and nitrogen atoms;

R^1, R^2, R^3, R^4, and R^5 may be the same or different, and are each independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted aryl, alkoxy, amino, alkyl,

alkenyl, alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, heteroarylaminocarbonyl groups, and groups of formula IIA or IIB;



IIA



IIB

wherein R^1 may be absent if W is a nitrogen atom;

wherein R^2 may be absent if X is a nitrogen atom;

wherein R^3 may be absent if Z is a nitrogen atom;

wherein R^4 may be absent if Y is a nitrogen atom;

wherein R^5 may be absent if Q is a nitrogen atom;

wherein one of R^1, R^2, R^3, R^4, or R^5 is a group having the formula IIA or IIB;

$R^{1'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

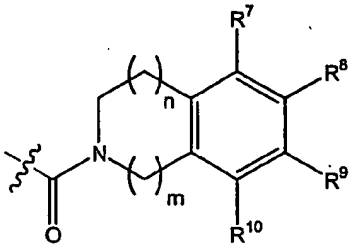
$R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups; or

$R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl or heteroaryl group;

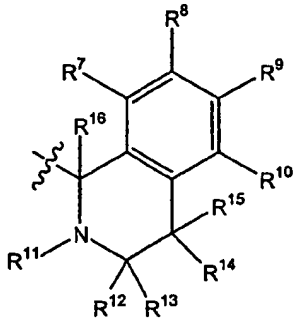
$R^{3'}$ is selected from the group consisting of substituted and unsubstituted aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

$R^{4'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, and heteroarylalkyl groups;

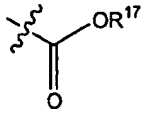
R^6 is a group of formula IIIA, IIIB, IIIC, IIID, or IIIE;



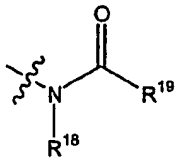
IIIA



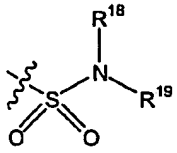
IIIB



IIIC



IIID



IIIE

m is an integer selected from 0, 1, or 2;

n is an integer selected from 0, 1, or 2;

R^7, R^8, R^9, and R^{10} may be the same or different and are independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted alkoxy, amino, alkyl, aryl, alkenyl,

alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, and heteroarylaminocarbonyl groups;

R^7 and R^8 may join together with the carbon atoms to which they are attached to form a substituted or unsubstituted 5 or 6 membered ring;

R^{11} is selected from the group consisting of H, and substituted and unsubstituted alkyl groups;

R^{12}, R^{13}, R^{14}, and R^{15} may be the same or different and are each independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted alkoxy, amino, alkyl, aryl, alkenyl, alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, and heteroarylaminocarbonyl groups;

R^{12} and R^{14} may represent a second bond between the carbon bonded to R^{12} and the carbon bonded to R^{14} such that the bond between the carbon bonded to R^{12} and the carbon bonded to R^{14} is a double bond; and

R^{16} is selected from the group consisting of H, and substituted and unsubstituted alkyl groups;

R^{11} and R^{16} may represent a second bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} such that the bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} is a double bond;

R^{17} is selected from the group consisting of H, and substituted and unsubstituted arylalkyl , heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups;

R^{18} is selected from the group consisting of H, and substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups; and

R^{19} is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups.

Compounds provided by the invention further include prodrugs of the compound of formula I, pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, hydrates thereof, hydrides thereof, or solvates thereof.

In one embodiment R^6 has the formula IIIA. In some embodiments where R^6 has the formula IIIA, m is 0 and n is 2. In other embodiments where R^6 has the formula IIIA, m is 1 and n is 1. In still other embodiments where R^6 has the formula IIIA, m is 0 and n is 1. In yet other embodiments where R^6 has the formula IIIA, m is 2 and n is 1.

In another embodiment R^6 has the formula IIIB. In some embodiments where R^6 has the formula IIIB, R^{11} and R^{16} represent a second bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} such that the bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} is a double bond. In other embodiments where R^6 has the formula IIIB, R^{11} is H or a substituted or unsubstituted alkyl group and R^{16} is H.

In other embodiments in which R^6 is a group of formula IIIA or IIIB, at least one of R^8 or R^9 is selected from the group consisting of Br, Cl, F, I substituted and unsubstituted alkyl groups, and substituted and unsubstituted alkoxy groups.

The invention provides further compounds of formula I in which R^6 has the formula IIIC.

The invention provides further compounds of formula I in which R^6 has the formula IIID. In other embodiments, R^6 has the formula IIIE. In some embodiments in which R^6 has the formula IIID or IIIE, R^{18} is H. In other embodiments in which R^6 has the formula IIID, R^{19} is a substituted arylalkyl group, and the alkyl group of the R^{19} arylalkyl group is substituted with an amino or acetamido group.

In other embodiments in which R^6 is a group of formula IIIC, IIID or IIIE, R^{17} or R^{19} is selected from the group consisting of substituted and unsubstituted arylalkyl groups, and substituted and unsubstituted heteroarylalkyl groups. In other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is a substituted or unsubstituted phenylalkyl group or a substituted or unsubstituted indolylalkyl group. In still other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is a 2,4-disubstituted phenylethyl group or an indolylethyl group. In still other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is selected from the group consisting of 2,4-dihalophenylethyl, and 2,4-dialkylphenylethyl groups. In still other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is selected from the group consisting of phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 2-fluoro-4-bromophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-fluorophenylethyl, 2,4-difluorophenylethyl, 2,4-dimethylphenylethyl, or 2,4-dimethoxyphenylethyl groups. In some embodiments such as those described above in which R^{17} or R^{19} is a substituted or unsubstituted arylalkyl group such as a substituted or unsubstituted arylethyl group or more specifically a substituted phenylethyl group, the alkyl or ethyl group of the substituted or unsubstituted arylalkyl

group is further substituted with a group such as an amino group; an alkylamino group such as a methylamino group; a hydroxyalkyl group such as a hydroxymethyl group; an –N(H)C(=O)-alkyl group such as a -N(H)C(=O)-CH_3 group; an –N(H)C(=O)-O-alkyl group such as a -N(H)C(=O)-O-$C(CH_3)_3$ group; or an -N(H)C(=O)-O-arylalkyl group such as a -N(H)C(=O)-O-benzyl group; an -N(H)C(=O)-heterocyclyl group such as a -N(H)C(=O)-(1,2,3,4-tetrahydroisoquinoline) group; or an arylalkoxyalkyl group, such as a phenylmethoxymethyl group, a 3-bromophenylmethoxy-methyl group, a 4-methylphenylmethoxymethyl group, a 4-fluorophenylmethoxymethyl group, a 2-fluoro-4-chlorophenylmethoxymethyl group, and the like.

In other embodiments having any of the features described above, Q is a carbon atom and R^5 is a group having the formula IIA or IIB.

In some embodiments, Q, W, X, Y, and Z are all carbon atoms whereas in other embodiments one of Q, W, X, Y, or Z is a nitrogen atom such that the ring containing Q, W, X, Y, and Z is a pyridine ring.

In other embodiments having any of the features described above, $R^{4'}$ is H.

Other embodiments are provided which have any of the features described above in which $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cycloalkyl, polycyclic cycloalkyl, alkenyl, alkyl, and aryl groups. In still other embodiments, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-alkylcyclohexyl, 2,2-dialkylcyclohexyl, 2,3-dialkylcyclohexyl, 2,4-dialkylcyclohexyl, 2,5-dialkylcyclohexyl, 2,6-dialkylcyclohexyl, 3,4-dialkylcyclohexyl, 3-alkylcyclohexyl, 4-alkylcyclohexyl, 3,3,5-trialkylcyclohexyl, cyclohexylmethyl, 2-aminocyclohexyl, 3-aminocyclohexyl, 4-aminocyclohexyl, 2,3-diaminocyclohexyl, 2,4-diaminocyclohexyl, 3,4-diaminocyclohexyl, 2,5-diaminocyclohexyl, 2,6-diaminocyclohexyl, 2,2-diaminocyclohexyl, 2-

alkoxycyclohexyl, 3-alkoxycyclohexyl, 4-alkoxycyclohexyl, 2,3-dialkoxycyclohexyl, 2,4-dialkoxycyclohexyl, 3,4-dialkoxycyclohexyl, 2,5-dialkoxycyclohexyl, 2,6-dialkoxycyclohexyl, 2,2-dialkoxycyclohexyl, 2-alkylthiocyclohexyl, 3-alkylthiocyclohexyl, 4-alkylthiocyclohexyl, 2,3-dialkylthiocyclohexyl, 2,4-dialkylthiocyclohexyl, 3,4-dialkylthiocyclohexyl, 2,5-dialkylthiocyclohexyl, 2,6-dialkylthiocyclohexyl, 2,2-dialkylthiocyclohexyl, cyclopentyl, cycloheptyl, cyclohexenyl, isopropyl, n-butyl, cyclooctyl, 2-arylcyclohexyl, 2-phenylcyclohexyl, 2-arylalkylcyclohexyl, 2-benzylcyclohexyl, 4-phenylcyclohexyl, adamantyl, isocamphenyl, carenyl, 7,7-dialkylnorbornyl, bornyl, norbornyl, and decalinyl groups. In still other embodiments, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-methylcyclohexyl, 2,2-dimethylcyclohexyl, 2,3-dimethylcyclohexyl, 2,4-dimethylcyclohexyl, 2,5-dimethylcyclohexyl, 2,6-dimethylcyclohexyl, 3,4-dimethylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, cyclohexenyl, 3,3,5-trimethylcyclohexyl, 4-*t*-butylcyclohexyl, cyclohexylmethyl, isopinocampheyl, 7,7-dimethylnorbornyl, 4-isopropylcyclohexyl, and 3-methylcycloheptyl groups. In some embodiments, $R^{3'}$ is a substituted cyclohexyl group such as a trifluoromethyl substituted cyclohexyl group such as a 4-trifluoromethylcyclohexyl group.

Other embodiments are provided which have any of the features described above in which $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups. In still other embodiments, $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups. In still further embodiments, $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups. In yet other embodiments, $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and

unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups. In still other embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl group. In other embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted saturated heterocyclyl group comprising at least one heteroatom selected from the group consisting of O, S, and N, in addition to the nitrogen atom to which $R^{1'}$ and $R^{2'}$ are bound. In yet other embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted piperazino, morpholino, pyrrolidino, piperidino, homopiperazino, or azepino group. In still further embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazino group optionally substituted by one or two methyl groups.

In some embodiments, if R^{17} is H or an unsubstituted alkyl group, then $R^{1'}$ and $R^{2'}$ join together, with the nitrogen atom to which they are bound, to form a substituted or unsubstituted heterocyclyl group. In some such embodiments, $R^{3'}$ is a substituted cycloalkyl group or a substituted polycyclic cycloalkyl group. In other such embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are bound, form a substituted or unsubstituted heterocyclyl group that additionally includes an O, S, or an additional N atom. In some such embodiments $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are bound, form a substituted or unsubstituted piperazino, morpholino, pyrrolidino, piperidino, homopiperazino, or azepino group.

There has also been provided, in accordance with another aspect of the invention, a composition comprising a compound according to the instant invention and a pharmaceutically acceptable carrier.

There has also been provided, in accordance with another aspect of the invention, a method of treating an MC4-R mediated disease,

comprising administering to a subject in need thereof, a compound or composition of the instant invention.

In one embodiment, a disease to be treated by those methods of the instant invention is obesity or type II diabetes.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

Detailed Description of the Preferred Embodiment

The instant invention relates to novel classes of small molecule melanocortin-4 receptor (MC4-R) agonists. These compounds can be formulated into compositions and are useful in activating MC4-R, or in the treatment of MC4-R-mediated diseases, such as obesity, type II diabetes, erectile dysfunction, polycystic ovary disease, complications resulting from or associated with obesity and diabetes, and Syndrome X.

The following definitions are used throughout this specification.

Alkyl groups include straight chain and branched alkyl groups having 1 to about 8 carbon atoms. Examples of straight chain alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl groups. Examples of branched alkyl groups, include, but not limited to, isopropyl, sec-butyl, t-butyl, and isopentyl groups. Representative substituted alkyl groups may be substituted one or more times with, for example, amino, thio, alkoxy, or halo groups such as F, Cl, Br, and I groups.

Cycloalkyl groups are cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. Cycloalkyl groups also includes rings that are substituted with straight or branched chain alkyl groups as defined above, and further include cycloalkyl groups that are substituted with other rings including fused rings such as, but not limited to, decalinyl, tetrahydronaphthyl, and indanyl. Cycloalkyl groups also include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups. Representative substituted cycloalkyl groups may be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or cycloheptyl groups, which may be substituted with, for example, alkyl, alkoxy, amino, thio, or halo groups.

Alkenyl groups are straight chain, branched or cyclic lower alkyl groups having 2 to about 8 carbon atoms, and further including at least one double bond, as exemplified, for instance, by vinyl, propenyl, 2-butenyl, 3-butenyl, isobutenyl, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl groups among others.

Alkynyl groups are straight chain or branched lower alkyl groups having 2 to about 8 carbon atoms, and further including at least one triple bond, as exemplified by groups, including, but not limited to, ethynyl, propynyl, and butynyl groups.

Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. Thus aryl groups include, but are not limited to, phenyl, azulene, heptalene, biphenylene, indacene, fluorene, phenanthrene, triphenylene, pyrene, naphthacene, chrysene, biphenyl, anthracenyl, and naphthenyl groups. Although the phrase "aryl groups" includes groups containing fused rings, such as fused aromatic-aliphatic ring systems, it does not include aryl groups that have other groups, such as alkyl or halo groups, bonded to one of the ring members. Rather, groups such as tolyl are referred

to as substituted aryl groups. The phrase "aryl groups" includes groups bonded to one or more carbon atom(s), and/or nitrogen atom(s), in the compounds of formulas I and II. Representative substituted aryl groups may be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or benzyl groups, which may be substituted with groups including, but not limited to, amino, alkoxy, alkyl, or halo.

Cycloalkylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a cycloalkyl group as defined above.

Arylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above.

Heterocyclyl groups are nonaromatic ring compounds containing 3 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. The phrase "heterocyclyl group" includes fused ring species including those comprising fused aromatic and nonaromatic groups. The phrase also includes polycyclic ring systems containing a heteroatom such as, but not limited to quinuclidyl. However, the phrase does not include heterocyclyl groups that have other groups, such as alkyl or halo groups, bonded to one of the ring members. Rather, these are referred to as "substituted heterocyclyl groups". Heterocyclyl groups include, but are not limited to, piperazino, morpholino, thiomorpholino, pyrrolidino, piperidino and homopiperazino groups. Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to morpholino or piperazino groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with groups including, but not limited to, amino, alkoxy, alkyl, or halo.

Heteroaryl groups are aromatic ring compounds containing 3 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Heteroaryl groups include, but are not limited to, groups such as furan, thiophene, pyrrole, isopyrrole, diazole, imidazole, isoimidazole, triazole, dithiole, oxathiole, isoxazole, oxazole, thiazole, isothiazole, oxadiazole, oxatriazole, dioxazole, oxathiazole, pyran, dioxin, pyridine, pyrimidine, pyridazine, pyrazine, triazine, oxazine, isoxazine, oxathiazine, azepin, oxepin, thiepin, diazepine, benzofuran, and isobenzofuran. Although the phrase "heteroaryl groups" includes fused ring compounds, the phrase does not include heteroaryl groups that have other groups bonded to one of the ring members, such as alkyl groups. Rather, heteroaryl groups with such substitution are referred to as "substituted heteroaryl groups". Representative substituted heteroaryl groups may be substituted one or more times with groups including, but not limited to, amino, alkoxy, alkyl, or halo.

Heterocyclylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heterocyclyl group as defined above.

Heteroarylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined above.

Aminocarbonyl groups are groups of the formula RR'NC(O)-, wherein R or R' may be the same or different, and each is independently selected from H, or substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl groups, as defined above.

In general, "substituted" refers to a group as defined above in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms such as, but not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as

hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups and also substituted cycloalkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a bond to a heteroatom such as oxygen in carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles.

Substituted cycloalkyl, substituted aryl, substituted heterocyclyl and substituted heteroaryl also include rings and fused ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, substituted aryl, substituted heterocyclyl and substituted heteroaryl groups may be substituted with alkyl groups as defined above.

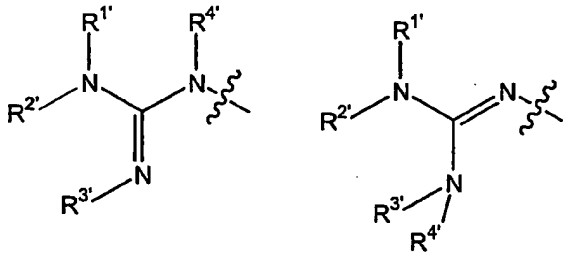
Pharmaceutically acceptable salts include a salt with an inorganic base, organic base, inorganic acid, organic acid, or basic or acidic amino acid. As salts of inorganic bases, the invention includes, for example, alkali metals such as sodium or potassium, alkali earth metals such as calcium and magnesium or aluminum, and ammonia. As salts of organic bases, the invention includes, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine. As salts of inorganic acids, the instant invention includes, for example, hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid. As salts of organic acids, the instant invention includes, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid. As salts of basic amino acids, the instant

invention includes, for example, arginine, lysine and ornithine. Acidic amino acids include, for example, aspartic acid and glutamic acid.

Prodrugs, as used in the context of the instant invention, includes those derivatives of the instant compounds which undergo in vivo metabolic biotransformation, by enzymatic or nonenzymatic processes, such as hydrolysis, to form a compound of the invention. Prodrugs can be employed to improve pharmaceutical or biological properties, as for example solubility, melting point, stability and related physicochemical properties, absorption, pharmacodynamics and other delivery-related properties.

The instant invention provides potent and specific agonists of MC4-R that are low molecular weight small molecules. In accordance with one aspect of the invention, the invention provides compounds of A^1-A^2-A^3-A^4. Compounds of the invention further include prodrugs of compounds of formula A^1-A^2-A^3-A^4, pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, hydrates thereof, hydrides thereof, or solvates thereof.

In compounds of formula A^1-A^2-A^3-A^4, A^1 is a group of formula IIA or IIB.



IIA IIB

In compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups, and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups. In compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are both bound, may alternatively form a substituted or unsubstituted heterocyclyl or heteroaryl group. In one embodiment of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups. In still further embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups. In yet other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl group. In other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted saturated heterocyclyl group comprising at least one heteroatom selected from the group consisting of O, S, and N, in addition to the nitrogen atom to which $R^{1'}$ and $R^{2'}$ are bound. In another embodiment of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are bound, form a substituted or unsubstituted heterocyclyl ring containing at least two nitrogen atoms. In still another embodiment of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are bound, form a substituted or unsubstituted heterocyclyl ring containing at least one oxygen atom and one nitrogen atom.

In yet other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted piperazino, morpholino, pyrrolidino, piperidino, homopiperazino, or azepino group. In still further embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazino group optionally substituted by one or two alkyl groups or in one embodiment by one or two methyl groups.

In compounds of formula A^1-A^2-A^3-A^4, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups. In one embodiment of compounds of formula A^1-A^2-A^3-A^4, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cycloalkyl, polycyclic cycloalkyl, alkenyl, alkyl, and aryl groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-alkylcyclohexyl, 2,2-dialkylcyclohexyl, 2,3-dialkylcyclohexyl, 2,4-dialkylcyclohexyl, 2,5-dialkylcyclohexyl, 2,6-dialkylcyclohexyl, 3,4-dialkylcyclohexyl, 3-alkylcyclohexyl, 4-alkylcyclohexyl, 3,3,5-trialkylcyclohexyl, cyclohexylmethyl, 2-aminocyclohexyl, 3-aminocyclohexyl, 4-aminocyclohexyl, 2,3-diaminocyclohexyl, 2,4-diaminocyclohexyl, 3,4-diaminocyclohexyl, 2,5-diaminocyclohexyl, 2,6-diaminocyclohexyl, 2,2-diaminocyclohexyl, 2-alkoxycyclohexyl, 3-alkoxycyclohexyl, 4-alkoxycyclohexyl, 2,3-dialkoxycyclohexyl, 2,4-dialkoxycyclohexyl, 3,4-dialkoxycyclohexyl, 2,5-dialkoxycyclohexyl, 2,6-dialkoxycyclohexyl, 2,2-dialkoxycyclohexyl, 2-alkylthiocyclohexyl, 3-alkylthiocyclohexyl, 4-alkylthiocyclohexyl, 2,3-dialkylthiocyclohexyl, 2,4-dialkylthiocyclohexyl, 3,4-dialkylthiocyclohexyl, 2,5-dialkylthiocyclohexyl, 2,6-dialkylthiocyclohexyl, 2,2-dialkylthiocyclohexyl, cyclopentyl, cycloheptyl, cyclohexenyl, isopropyl, n-butyl, cyclooctyl, 2-arylcyclohexyl, 2-phenylcyclohexyl, 2-arylalkylcyclohexyl, 2-benzylcyclohexyl, 4-phenylcyclohexyl, adamantyl, isocamphenyl, carenyl, 7,7-dialkylnorbornyl, bornyl, norbornyl, and decalinyl groups. In still other embodiments of

compounds of formula A^1-A^2-A^3-A^4, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-methylcyclohexyl, 2,2-dimethylcyclohexyl, 2,3-dimethylcyclohexyl, 2,4-dimethylcyclohexyl, 2,5-dimethylcyclohexyl, 2,6-dimethylcyclohexyl, 3,4-dimethylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, cyclohexenyl, 3,3,5-trimethylcyclohexyl, 4-*t*-butylcyclohexyl, cyclohexylmethyl, isopinocampheyl, 7,7-dimethylnorbornyl, 4-isopropylcyclohexyl, and 3-methylcycloheptyl groups.

In compounds of formula A^1-A^2-A^3-A^4, $R^{4'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, and heteroarylalkyl groups. In one embodiment of compounds of formula A^1-A^2-A^3-A^4, $R^{4'}$ is H.

In compounds of formula A^1-A^2-A^3-A^4, A^2 is selected from the group consisting of substituted and unsubstituted aryl groups and substituted and unsubstituted heteroaryl groups. In one embodiment of compounds of formula A^1-A^2-A^3-A^4, A^2 is selected from the group consisting of substituted and unsubstituted phenyl groups and substituted and unsubstituted pyridyl groups. In another embodiment, A^2 is a substituted or unsubstituted phenyl group and A^1 and A^3 are ortho to one another on the A^2 phenyl group. In another embodiment, A^2 is a substituted or unsubstituted phenyl group and A^1 and A^3 are para to one another on the A^2 phenyl group. In another embodiment, A^2 is a substituted or unsubstituted phenyl group and A^1 and A^3 are meta to one another on the A^2 phenyl group. In another embodiment, A^2 is a substituted or unsubstituted phenyl group, A^3 is a covalent bond, and A^1 and A^4 are ortho to one another on the A^2 phenyl group. In another embodiment, A^2 is a substituted or unsubstituted phenyl group, A^3 is a covalent bond, and A^1 and A^4 are para to one another on the A^2 phenyl group. In yet another embodiment, A^2 is a substituted or unsubstituted phenyl group, A^3 is a covalent bond, and A^1 and A^4 are meta to one another on the A^2 phenyl group.

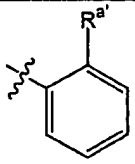
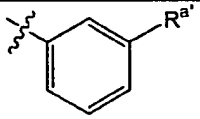
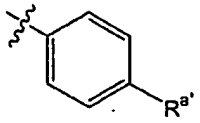
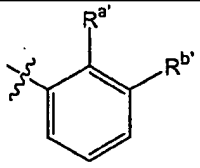
In compounds of formula A^1-A^2-A^3-A^4, A^3 is a covalent bond such that A^2 is directly bonded to A^4. Alternatively, in compounds of formula A^1-A^2-A^3-A^4, A^3 is a linking group selected from the group consisting of O, S, -NR^a-, -C(=O)-, -C(=O)O-, -NR^aC(=O)-, -SO_2NR^a-, -C(=S)-, -C(=O)S-, -P(=O)R^b-, -SO_2-, and -S(=O)-. If A^3 is a linking group, then it is bonded to A^2 and A^4 in a configuration selected from the group consisting of A^2-O-A^4, A^2-S-A^4, A^2-NR^a-A^4, A^2-C(=O)-A^4, A^2-C(=O)O-A^4, A^4-C(=O)O-A^2, A^2-NR^aC(=O)-A^4, A^4-NR^aC(=O)-A^2, A^2-SO_2NR^a-A^4, A^4-SO_2NR^a-A^2, A^2-C(=S)-A^4, A^2-(C=O)S-A^4, A^4-(C=O)S-A^2, A^2-(P=O)R^b-A^4, A^2-SO_2-A^4, and A^2-S(=O)-A^4. In compounds of formula A^1-A^2-A^3-A^4, if A^3 is a linking group with the configuration A^4-NR^aC(=O)-A^2, then A^2 is not a substituted or unsubstituted phenyl group and is not a substituted or unsubstituted 6-membered N-containing heteroaryl group. In one embodiment of compounds of formula A^1-A^2-A^3-A^4, A^3 is a linking group such that A^2 is directly bonded to A^4. In some embodiments, A^3 is a linking group bonded to A^2 and A^4 in a configuration selected from the group consisting of A^2-NR^a-A^4, A^2-C(=O)-A^4, A^2-C(=O)O-A^4, A^4-C(=O)O-A^2, A^2-NHC(=O)-A^4, A^2-SO_2NH-A^4, and A^2-SO_2-A^4.

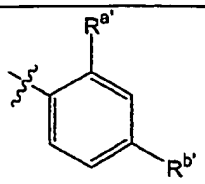
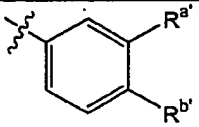
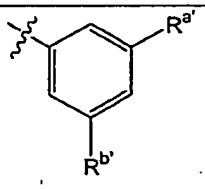
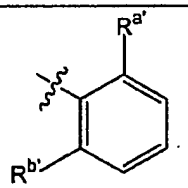
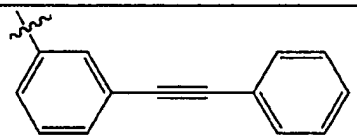
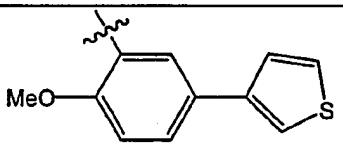
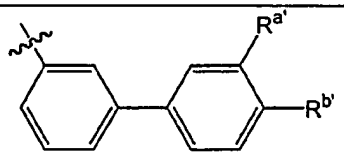
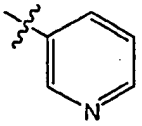
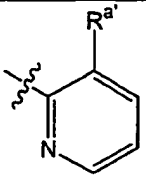
In compounds of formula A^1-A^2-A^3-A^4, A^4 is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups. In one embodiment of compounds of formula A^1-A^2-A^3-A^4, A^4 is a 2,4-disubstituted phenylethyl group or an indolylethyl group. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, A^4 is selected from the group consisting of 2,4-dihalophenylethyl, and 2,4-dialkylphenylethyl groups. In still other embodiments of compounds of formula A^1-A^2-A^3-A^4, A^4 is selected from the group consisting of phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenyl-ethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-

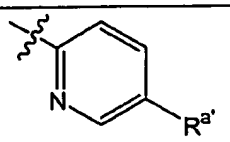
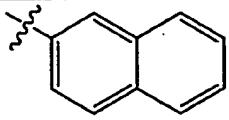
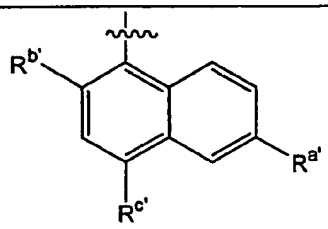
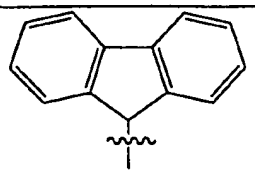
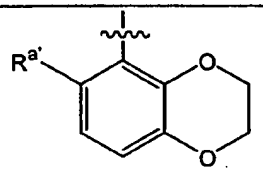
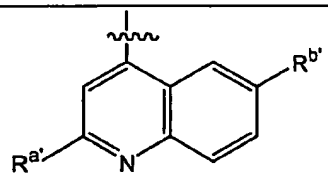
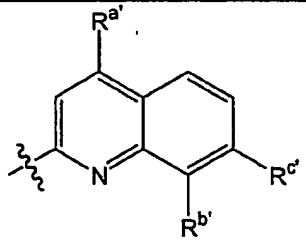
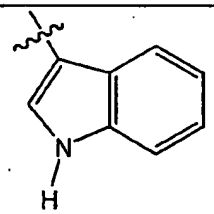
dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 2-fluoro-4-bromophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-fluorophenylethyl, 2,4-difluorophenylethyl, 2,4-dimethylphenylethyl, or 2,4-dimethoxyphenylethyl groups.

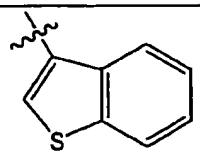
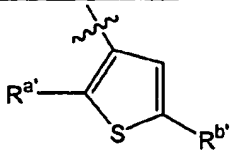
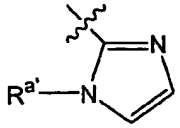
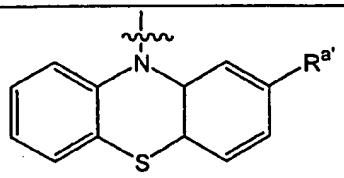
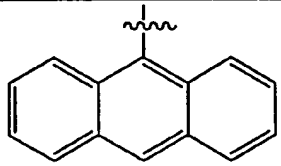
In some embodiments of compounds of formula A^1-A^2-A^3-A^4, A^4 is a substituted or unsubstituted arylalkyl or heteroarylalkyl group such as a substituted arylethyl, arylmethyl, heteroarylethyl, or heteroarylmethyl group, where the aryl or heteroaryl group is a group such as one of those included in Table I. In Table 1, Bn is benzyl, Cp is cyclopentyl, Pr is propyl, iPr is isopropyl, Et is ethyl, Me is methyl, Ph is phenyl, and t-Bu is t-butyl.

Table 1.

Aryl/Heteroaryl Group	$R^{a'}$, $R^{b'}$
	$R^{a'}$ = -H, -Cl, -F, -Br, -I, -CN, -Me, -Ph, -NHMe, -SH, -SMe, -OMe, $-CH_2SO_2Ph$, or -OCp
	$R^{a'}$ = -F, -Cl, -Br, -I, -CN, $-NO_2$, -CN, -OMe, -Me, or -Ph
	$R^{a'}$ = -F, -Cl, -Br, -I, -OMe, -OBn, $-CF_3$, -CN, $-NO_2$, -Me, -Ph, or -tBu
	$R^{a'}$ = -OMe; and $R^{b'}$ = -OMe

	$R^{a'}$ = -OMe, -OEt, -OPr, -OiPr, -OCp, $-CF_3$, -Me, -Br, or -Cl; and $R^{b'}$ = -OMe, -Me, -Ph, -tBu, -F, -Cl, -Br, -I, $-NO_2$, -CN, $-CF_3$, or $-C(=O)CH_3$
	$R^{a'}$ = -Me or -Cl; and $R^{b'}$ = -Me or -Cl
	$R^{a'}$ = $-CF_3$ or -OMe; and $R^{b'}$ = $-CF_3$ or -OMe
	$R^{a'}$ = -F, -Cl, or -OMe; and $R^{b'}$ = -F, -Cl, OMe, or -Br
	Not Applicable
	Not Applicable
	$R^{a'}$ = -H or -Cl; and $R^{b'}$ = -OMe or –F
	Not Applicable
	$R^{a'}$ = H or CF_3

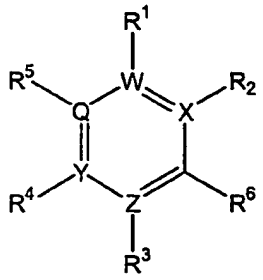
	$R^{a'}$ = H or CF_3
	Not Applicable
	$R^{a'}$ = -H, -F, or –Br; $R^{b'}$ = -H, -OMe, -OEt, -OPr, -OiPr, or –OCp; and $R^{c'}$ = -H, -F, or –Me
	Not Applicable
	$R^{a'}$ = -H or -OMe
	$R^{a'}$ = -H, -Cl, or -CF_3; and $R^{b'}$ = -H or -Br
	$R^{a'}$ = -H or -Me; $R^{b'}$ = -H or -Me; and $R^{c'}$ = -H or -Cl
	Not applicable

	Not applicable
	$R^{a'}$ = -H or -Cl; and $R^{b'}$ = -H or -Cl
	$R^{a'}$ = -H or -OBn
	$R^{a'}$ = -H or -SMe
	Not applicable

In compounds of formula A^1-A^2-A^3-A^4, R^a is selected from the group consisting of H, and substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups. In one embodiment of compounds of formula A^1-A^2-A^3-A^4, R^a is H.

In compounds of formula A^1-A^2-A^3-A^4, R^b is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups.

In accordance with one aspect of the invention, the invention provides a first group of compounds of formula I such as shown below.



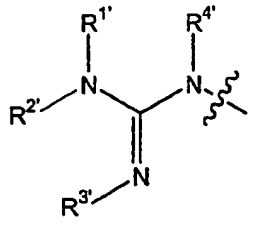
I

Compounds of the invention further include prodrugs of the first group of compounds of formula I, pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, hydrates thereof, hydrides thereof, or solvates thereof.

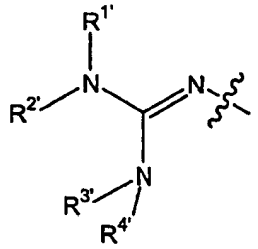
In the first group of compounds of formula I, Q, W, X, Y, and Z are independently selected from the group consisting of carbon atoms and nitrogen atoms. In some embodiments of the compounds of formula I, at least one of Q, W, X, Y, and Z is a nitrogen atom. In other embodiments of the compounds of formula I, Q, W, X, Y, and Z are all carbon atoms. In other embodiments of the compounds of formula I, Q is a nitrogen atom and W, X, Y, and Z are all carbon atoms. In other embodiments of the compounds of formula I, W is a nitrogen atom and Q, X, Y, and Z are all carbon atoms. In other embodiments of the compounds of formula I, X is a nitrogen atom and Q, W, Y, and Z are all carbon atoms. In still other embodiments of the compounds of formula I, Y is a nitrogen atom and Q, W, X, and Z are all carbon atoms. In still other embodiments of the compounds of formula I, Z is a nitrogen atom and Q, W, X, and Y are all carbon atoms.

In the first group of compounds of formula I, R^1, R^2, R^3, R^4, and R^5 may be the same or different, and are each independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted aryl, alkoxy, amino, alkyl, alkenyl, alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl,

arylaminocarbonyl, heterocyclylaminocarbonyl, heteroarylaminocarbonyl groups, and groups of formula IIA or IIB.



IIA



IIB

In the first group of compounds of formula I, R^1 may be absent if W is a nitrogen atom; R^2 may be absent if X is a nitrogen atom; R^3 may be absent if Z is a nitrogen atom;R^4 may be absent if Y is a nitrogen atom; and R^5 may be absent if Q is a nitrogen atom. In the first group of compounds of formula I, at least one of R^1, R^2, R^3, R^4, or R^5 is a group having the formula IIA or IIB. In some embodiments of the first group of compounds of formula I, Q is a carbon atom and R^5 is a group having the formula IIA or IIB. In one embodiment, four of R^1 through R^5 are H, and one of R^1 through R^5 is a group of formula IIA or IIB. In other embodiments, three of R^1 through R^5 are H, one of R^1 through R^5 is absent, one of R^1 through R^5 is a group of formula IIA or IIB, one of W, Q, X, Y, and Z is a nitrogen atom, and four of W, Q, X, Y, and Z are carbon atoms.

In the first group of compounds of formula I, $R^{1'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups, and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups. In the first group of compounds of formula I, $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are both bound, may alternatively form a substituted or unsubstituted heterocyclyl or heteroaryl group. In one embodiment $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of

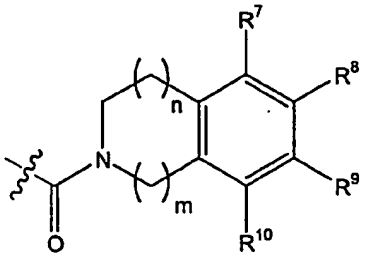
substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups. In still other embodiments, $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups. In still further embodiments, $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups. In yet other embodiments, $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups. In still other embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl group. In other embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted saturated heterocyclyl group comprising at least one heteroatom selected from the group consisting of O, S, and N, in addition to the nitrogen atom to which $R^{1'}$ and $R^{2'}$ are bound. In another embodiment, $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are bound, form a substituted or unsubstituted heterocyclyl ring containing at least two nitrogen atoms. In still another embodiment, $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are bound, form a substituted or unsubstituted heterocyclyl ring containing at least one oxygen atom and one nitrogen atom. In yet other embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted piperazino, morpholino, pyrrolidino, piperidino, homopiperazino, or azepino group. In still further embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazino group optionally substituted by one or two alkyl groups or in one embodiment by one or two methyl groups.

In the first group of compounds of formula I, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups. In one embodiment of the first group of compounds of formula I, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cycloalkyl, polycyclic cycloalkyl, alkenyl, alkyl, and aryl groups. In still other embodiments, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-alkylcyclohexyl, 2,2-dialkylcyclohexyl, 2,3-dialkylcyclohexyl, 2,4-dialkylcyclohexyl, 2,5-dialkylcyclohexyl, 2,6-dialkylcyclohexyl, 3,4-dialkylcyclohexyl, 3-alkylcyclohexyl, 4-alkylcyclohexyl, 3,3,5-trialkylcyclohexyl, cyclohexylmethyl, 2-aminocyclohexyl, 3-aminocyclohexyl, 4-aminocyclohexyl, 2,3-diaminocyclohexyl, 2,4-diaminocyclohexyl, 3,4-diaminocyclohexyl, 2,5-diaminocyclohexyl, 2,6-diaminocyclohexyl, 2,2-diaminocyclohexyl, 2-alkoxycyclohexyl, 3-alkoxycyclohexyl, 4-alkoxycyclohexyl, 2,3-dialkoxycyclohexyl, 2,4-dialkoxycyclohexyl, 3,4-dialkoxycyclohexyl, 2,5-dialkoxycyclohexyl, 2,6-dialkoxycyclohexyl, 2,2-dialkoxycyclohexyl, 2-alkylthiocyclohexyl, 3-alkylthiocyclohexyl, 4-alkylthiocyclohexyl, 2,3-dialkylthiocyclohexyl, 2,4-dialkylthiocyclohexyl, 3,4-dialkylthiocyclohexyl, 2,5-dialkylthiocyclohexyl, 2,6-dialkylthiocyclohexyl, 2,2-dialkylthiocyclohexyl, cyclopentyl, cycloheptyl, cyclohexenyl, isopropyl, n-butyl, cyclooctyl, 2-arylcyclohexyl, 2-phenylcyclohexyl, 2-arylalkylcyclohexyl, 2-benzylcyclohexyl, 4-phenylcyclohexyl, adamantyl, isocamphenyl, carenyl, 7,7-dialkylnorbornyl, bornyl, norbornyl, and decalinyl groups. In still other embodiments, $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-methylcyclohexyl, 2,2-dimethylcyclohexyl, 2,3-dimethylcyclohexyl, 2,4-dimethylcyclohexyl, 2,5-dimethylcyclohexyl, 2,6-dimethylcyclohexyl, 3,4-dimethylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, cyclohexenyl, 3,3,5-trimethylcyclohexyl, 4-*t*-butylcyclohexyl, cyclohexylmethyl, isopinocampheyl, 7,7-dimethylnorbornyl, 4-isopropylcyclohexyl, and 3-methylcycloheptyl groups. In some embodiments,

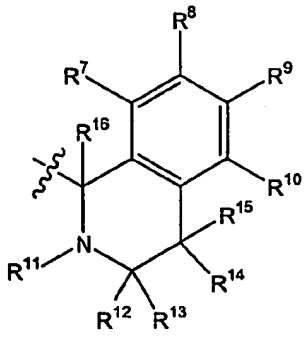
$R^{3'}$ is a substituted cyclohexyl group such as a trifluoromethyl substituted cyclohexyl group such as a 4-trifluoromethylcyclohexyl group.

In the first group of compounds of formula I, $R^{4'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, and heteroarylalkyl groups. In one embodiment, $R^{4'}$ is H.

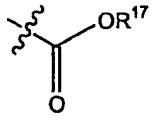
In the first group of compounds of formula I, R^6 is a group of formula IIIA, IIIB, IIIC, IIID, or IIIE.



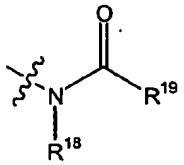
IIIA



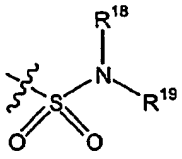
IIIB



IIIC



IIID

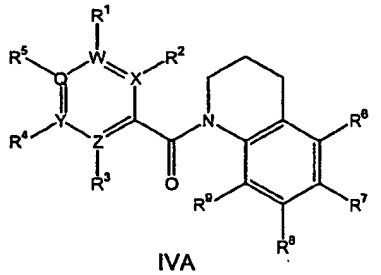


IIIE

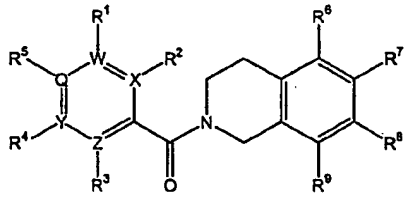
In some embodiments, R^6 has the formula IIIA. In other embodiments, R^6 has the formula IIIB. In still other embodiments, R^6 has the formula IIIC. In other embodiments, R^6 has the formula IIID. In still other embodiments, R^6 has the formula IIIE.

In the first group of compounds of formula I in which R^6 is a group of formula IIIA, m is an integer selected from 0, 1, or 2, and n is an

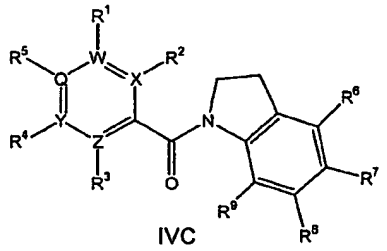
integer selected from 0, 1, or 2. In some embodiments where R^6 has the formula IIIA, m is 0 and n is 2. In other embodiments where R^6 has the formula IIIA, m is 1 and n is 1. In still other embodiments where R^6 has the formula IIIA, m is 0 and n is 1. In yet other embodiments where R^6 has the formula IIIA, m is 2 and n is 1. Examples of compounds in which m is 0 and n is 2, in which m is 1 and n is 1, in which m is 0 and n is 1, and in which m is 2 and n is 1 are respectively shown below as compounds of formula IVA, IVB, IVC, and IVD. In compounds of formula IVA through IVD, R^1 through R^5, R^7 through R^9, Q, W, X, Y, Z, and $R^{1'}$ through $R^{4'}$ have the same definitions set forth elsewhere in this document.



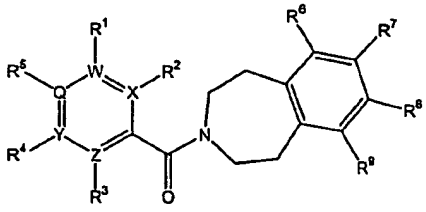
IVA



IVB



IVC



IVD

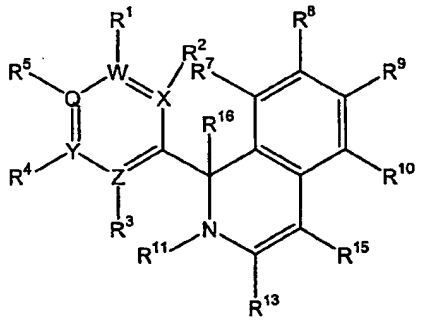
In the first group of compounds of formula I in which R^6 is a group of formula IIIA or IIIB, R^7, R^8, R^9, and R^{10} may be the same or different and are independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted alkoxy, amino, alkyl, aryl, alkenyl, alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, and heteroarylaminocarbonyl groups. In the first group of compounds of formula I in which R^6 is a group of formula IIIA or IIIB, R^7 and R^8 may alternatively join

together with the carbon atoms to which they are attached to form a substituted or unsubstituted 5 or 6 membered ring. In some embodiments in which R^6 is a group of formula IIIA or IIIB, at least one of R^8 or R^9 is selected form the group consisting of Br, Cl, F, I, and substituted and unsubstituted alkyl groups, and alkoxy groups.

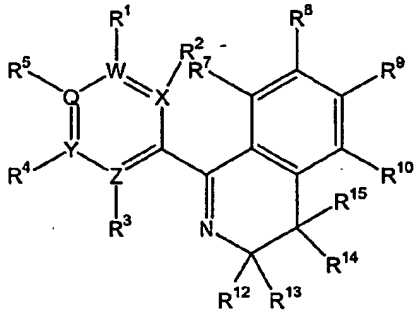
In the first group of compounds of formula I in which R^6 is a group of formula IIIB, R^{11} is selected from the group consisting of H, and substituted and unsubstituted alkyl groups.

In the first group of compounds of formula I in which R^6 is a group of formula IIIB, R^{12}, R^{13}, R^{14}, and R^{15} may be the same or different and are independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted alkoxy, amino, alkyl, aryl, alkenyl, alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, and heteroarylaminocarbonyl groups. In the first group of compounds of formula I in which R^6 is a group of formula IIIB, R^{16} is selected from the group consisting of H, and substituted and unsubstituted alkyl groups. In the first group of compounds of formula I in which R^6 is a group of formula IIIB, R^{12} and R^{14} may alternatively represent a second bond between the carbon bonded to R^{12} and the carbon bonded to R^{14} such that the bond between the carbon bonded to R^{12} and the carbon bonded to R^{14} is a double bond or is a bond of an aromatic ring. Such compounds have the formula VA. Furthermore, in the first group of compounds of formula I in which R^6 is a group of formula IIIB, R^{11} and R^{16} may represent a second bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} such that the bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} is a double bond or is a bond of an aromatic ring. Such compounds have the formula VB. In still other compounds of formula I, R^{12} and R^{14} represent a second bond between the carbon bonded to R^{12} and the carbon bonded to R^{14} such that the bond between the carbon bonded to R^{12} and the carbon bonded to R^{14} is

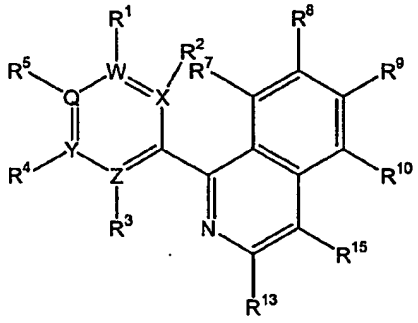
a double bond or is a bond of an aromatic ring, and R^{11} and R^{16} represent a second bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} such that the bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} is a double bond or is a bond of an aromatic ring.. Such compounds have the formula VC. In some embodiments in which R^6 is a group of formula IIIB, R^{11} is H or a substituted or unsubstituted alkyl group, and R^{16} is H. The variables in the compounds of formula VA, VB, and VC have the same definitions as described elsewhere in this document.



VA



VB



VC

In the first group of compounds of formula I in which R^6 is a group of formula IIIC, R^{17} is selected from the group consisting of H, and substituted and unsubstituted arylalkyl , heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups. In some embodiments, if R^{17} is H or an unsubstituted alkyl group, then $R^{1'}$ and $R^{2'}$ join together, with the nitrogen atom to which they are

bound, to form a substituted or unsubstituted heterocyclyl group. In some such embodiments, $R^{3'}$ is a substituted cycloalkyl group or a substituted polycyclic cycloalkyl group. In other such embodiments, $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are bound, form a substituted or unsubstituted heterocyclyl group that additionally includes an O, S, or an additional N atom. In some such embodiments $R^{1'}$ and $R^{2'}$, together with the nitrogen atom to which they are bound, form a substituted or unsubstituted piperazino, morpholino, pyrrolidino, piperidino, homopiperazino, or azepino group.

In the first group of compounds of formula I in which R^6 is a group of formula IIID or IIIE, R^{18} is selected from the group consisting of H, and substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups. In some embodiments in which R^6 is a group of formula IIID, R^{18} is H. In some embodiments in which R^6 is a group of formula IIIE, R^{18} is H.

In the first group of compounds of formula I in which R^6 is a group of formula IIID or IIIE, R^{19} is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups. In some embodiments in which R^6 is a group of formula IIID, R^{19} is a substituted arylalkyl group, and the alkyl group of the R^{19} arylalkyl group is substituted with an amino or acetamido group.

In some embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is selected from the group consisting of substituted and unsubstituted arylalkyl, alkenyl, heteroarylalkyl, and heterocyclylalkyl groups. In other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is selected from the group consisting of substituted and unsubstituted arylalkyl groups, and substituted and unsubstituted heteroarylalkyl groups. In other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is a substituted or unsubstituted phenylalkyl group or a substituted or

unsubstituted indolylalkyl group. In still other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is a 2,4-disubstituted phenylethyl group or an indolylethyl group. In still other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is selected from the group consisting of 2,4-dihalophenylethyl, and 2,4-dialkylphenylethyl groups. In still other embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is selected from the group consisting of phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 2-fluoro-4-bromophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-fluorophenylethyl, 2,4-difluorophenylethyl, 2,4-dimethylphenylethyl, or 2,4-dimethoxyphenylethyl groups. In some embodiments such as those described above in which R^{17} or R^{19} is a substituted or unsubstituted arylalkyl group such as a substituted or unsubstituted arylethyl group or more specifically a substituted phenylethyl group, the alkyl or ethyl group of the substituted or unsubstituted arylalkyl group is further substituted with a group such as an amino group; an alkylamino group such as a methylamino group; a hydroxyalkyl group such as a hydroxymethyl group; an –N(H)C(=O)-alkyl group such as a -N(H)C(=O)-CH_3 group; an –N(H)C(=O)-O-alkyl group such as a -N(H)C(=O)-O-$C(CH_3)_3$ group; an -N(H)C(=O)-O-arylalkyl group such as a -N(H)C(=O)-O-benzyl group; an -N(H)C(=O)-heterocyclyl group such as a -N(H)C(=O)-(1,2,3,4-tetrahydroisoquinoline) group; or an arylalkoxyalkyl group, such as a phenylmethoxymethyl group, a 3-bromophenylmethoxy-methyl group, a 4-methylphenylmethoxymethyl group, a 4-fluorophenyl-methoxymethyl group, a 2-fluoro-4-chlorophenylmethoxymethyl group, and the like.

In some embodiments in which R^6 is a group of formula IIIC, IIID, or IIIE, R^{17} or R^{19} is a substituted or unsubstituted arylalkyl or heteroarylalkyl group such as a substituted arylethyl, arylmethyl, heteroarylethyl, or heteroarylmethyl group, the aryl or heteroaryl group is a group such as one of those included in Table I above.

There has also been provided, in accordance with another aspect of the invention, a composition comprising a compound according to the instant invention and a pharmaceutically acceptable carrier.

There has also been provided, in accordance with another aspect of the invention, a method of activating MC4-R in a subject, comprising administering to a subject in need thereof an effective amount of a compound or composition of the instant invention.

There has also been provided, in accordance with another aspect of the invention, a method of treating an MC4-R–mediated disease, comprising administering to a subject in need thereof, a compound or composition of the instant invention.

In one embodiment, a disease to be treated by those methods of the instant invention is obesity, or type I or type II diabetes.

In another embodiment, a condition to be treated by those methods of the instant invention is a condition associated with or a complication arising from obesity or type II diabetes.

In another embodiment, a condition to be treated by those methods of the instant invention is erectile dysfunction.

In another embodiment, a disease to be treated by those methods of the instant invention is polycystic ovary disease.

In another embodiment, a disease to be treated by those methods of the instant invention is Syndrome X.

The invention also includes tautomers of the instant compounds. The instant invention also includes prodrugs, pharmaceutically acceptable salts, stereoisomers, hydrates, hydrides, and solvates of these tautomers.

The instant compounds may exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers, atropisomers and geometric isomers. In some cases, one stereoisomer may be more active and/or may exhibit beneficial effects in comparison to other stereoisomer(s) or when separated from the other stereoisomer(s). However, it is well within the skill of the ordinary artisan to separate, and/or to selectively prepare said stereoisomers. Accordingly, "stereoisomers" of the instant invention necessarily includes mixtures of stereoisomers, individual stereoisomers, or optically active forms.

The instant invention also provides for compositions which may be prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers thereof, with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, to treat or ameliorate a variety of disorders. Examples of such disorders include, but are not limited to obesity, erectile disorders, cardiovascular disorders, neuronal injuries or disorders, inflammation, fever, cognitive disorders, sexual behavior disorders. A therapeutically effective dose further refers to that amount of one or more compounds of the instant invention sufficient to result in amelioration of symptoms of the disorder. The pharmaceutical compositions of the instant invention can be manufactured by methods well known in the art such as conventional granulating, mixing, dissolving, encapsulating, lyophilizing, emulsifying or levigating processes, among others. The compositions can be in the form of, for example, granules, powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. The instant compositions can be formulated for various routes of administration, for example, by oral administration, by intranasal administration, by transmucosal administration, by rectal administration, or subcutaneous administration as well as intrathecal, intravenous, intramuscular,

intraperitoneal, intranasal, intraocular or intraventricular injection. The compound or compounds of the instant invention can also be administered in a local rather than a systemic fashion, such as injection as a sustained release formulation. The following dosage forms are given by way of example and should not be construed as limiting the instant invention.

For oral, buccal, and sublingual administration, powders, suspensions, granules, tablets, pills, capsules, gelcaps, and caplets are acceptable as solid dosage forms. These can be prepared, for example, by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers thereof, with at least one additive or excipient such as a starch or other additive. Suitable additives or excipients are sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, sorbitol, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides, methyl cellulose, hydroxypropylmethyl-cellulose, and/or polyvinylpyrrolidone. Optionally, oral dosage forms can contain other ingredients to aid in administration, such as an inactive diluent, or lubricants such as magnesium stearate, or preservatives such as paraben or sorbic acid, or anti-oxidants such as ascorbic acid, tocopherol or cysteine, a disintegrating agent, binders, a thickeners, buffers, a sweeteners, flavoring agents or perfuming agents. Additionally, dyestuffs or pigments may be added for identification. Tablets and pills may be further treated with suitable coating materials known in the art.

Liquid dosage forms for oral administration may be in the form of pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, slurries and solutions, which may contain an inactive diluent, such as water. Pharmaceutical formulations may be prepared as liquid suspensions or solutions using a sterile liquid, such as, but not limited to, an oil, water, an alcohol, and combinations of these. Pharmaceutically suitable surfactants, suspending agents, emulsifying agents, may be added for oral or parenteral administration.

As noted above, suspensions may include oils. Such oils include, but are not limited to, peanut oil, sesame oil, cottonseed oil, corn oil and olive oil. Suspension preparation may also contain esters of fatty acids such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. Suspension formulations may include alcohols, such as, but not limited to, ethanol, isopropyl alcohol, hexadecyl alcohol, glycerol and propylene glycol. Ethers, such as but not limited to, poly(ethyleneglycol), petroleum hydrocarbons such as mineral oil and petrolatum; and water may also be used in suspension formulations.

For intranasal administration (*e.g.*, to deliver compounds to the brain), or administration by inhalation (*e.g.*, to deliver compounds through the lungs), the pharmaceutical formulations may be a solution, a spray, a dry powder, or aerosol containing any appropriate solvents and optionally other compounds such as, but not limited to, stabilizers, antimicrobial agents, antioxidants, pH modifiers, surfactants, bioavailability modifiers and combinations of these. Examples of intranasal formulations and methods of administration can be found in WO 01/41782, WO 00/33813, WO 91/97947, U.S. Patent No. 6,180,603, and U.S. Patent No. 5,624,898. A propellant for an aerosol formulation may include compressed air, nitrogen, carbon dioxide, or a hydrocarbon based low boiling solvent. The compound or compounds of the instant invention are conveniently delivered in the form of an aerosol spray presentation from a nebulizer or the like.

Injectable dosage forms generally include aqueous suspensions or oil suspensions which may be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms may be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils may be employed as solvents or suspending agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

For injection, the pharmaceutical formulation may be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these. The compounds may be formulated for parenteral administration by injection such as by bolus injection or continuous infusion. A unit dosage form for injection may be in ampoules or in multi-dose containers.

For rectal administration, the pharmaceutical formulations may be in the form of a suppository, an ointment, an enema, a tablet or a cream for release of compound in the intestines, sigmoid flexure and/or rectum. Rectal suppositories are prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts or tautomers of the compound, with acceptable vehicles, for example, cocoa butter or polyethylene glycol, which is present in a solid phase at normal storing temperatures, and present in a liquid phase at those temperatures suitable to release a drug inside the body, such as in the rectum. Oils may also be employed in the preparation of formulations of the soft gelatin type and suppositories. Water, saline, aqueous dextrose and related sugar solutions, and glycerols may be employed in the preparation of suspension formulations which may also contain suspending agents such as pectins, carbomers, methyl cellulose, hydroxypropyl cellulose or carboxymethyl cellulose, as well as buffers and preservatives.

Besides those representative dosage forms described above, pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant invention. Such excipients and carriers are described, for example, in "Remingtons Pharmaceutical Sciences" Mack Pub. Co., New Jersey (1991), which is incorporated herein by reference.

The formulations of the invention may be designed for to be short-acting, fast-releasing, long-acting, and sustained-releasing as described below. Thus, the pharmaceutical formulations may also be formulated for controlled release or for slow release.

The instant compositions may also comprise, for example, micelles or liposomes, or some other encapsulated form, or may be administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the pharmaceutical formulations may be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections or as implants such as stents. Such implants may employ known inert materials such as silicones and biodegradable polymers.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms. Specific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs. Any of the above dosage forms containing effective amounts are well within the bounds of routine experimentation and therefore, well within the scope of the instant invention. A therapeutically effective dose may vary depending upon the route of administration and dosage form. The preferred compound or compounds of the instant invention is a formulation that exhibits a high therapeutic index. The therapeutic index is the dose ratio between toxic and therapeutic effects which can be expressed as the ratio between LD_{50} and ED_{50}. The LD_{50} is the dose lethal to 50% of the population and the ED_{50} is the dose therapeutically effective in 50% of the population. The LD_{50} and ED_{50} are determined by standard pharmaceutical procedures in animal cell cultures or experimental animals.

The present invention also provides methods of enhancing MC4-R activity in a human or non-human animal. The method comprises

administering an effective amount of a compound, or composition, of the instant invention to said mammal or non-human animal. Effective amounts of the compounds of the instant invention include those amounts that activate MC4-R which are detectable, for example, by an assay described below in the illustrative Examples, or any other assay known by those skilled in the art that a detect signal transduction, in a biochemical pathway, through activation of G-protein coupled receptors, for example, by measuring an elevated cAMP level as compared to a control model. Accordingly, "activating" means the ability of a compound to initiate a detectable signal. Effective amounts may also include those amounts which alleviate symptoms of a MC4-R disorder treatable by activating MC4-R.

An MC4-R disorder, or MC4-R-mediated disease, which may be treated by those methods provided, include any biological disorder or disease in which MC4-R is implicated, or which inhibition of MC4-R potentiates a biochemical pathway that is defective in the disorder or disease state. Examples of such diseases are obesity, erectile disorders, cardiovascular disorders, neuronal injuries or disorders, inflammation, fever, cognitive disorders, type II diabetes, polycystic ovary disease, Syndrome X, complications from obesity and diabetes, and sexual behavior disorders. In a preferred embodiment, the instant invention provides compounds, compositions, and methods effective for reducing energy intake and body weight; reducing serum insulin and glucose levels; alleviating insulin resistance; and reducing serum levels of free fatty acids. Accordingly, the instant invention is particularly effective in treating those disorders or diseases associated with obesity or type II diabetes.

"Treating" within the context of the instant invention, therefore, means an alleviation of symptoms associated with a disorder or disease, or halt of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder. For example, within the context of obesity, successful treatment may include an alleviation of symptoms or halting the progression of the disease, as measured by reduction in body

weight, or a reduction in amount of food or energy intake. In this same vein, successful treatment of type I or type II diabetes may include an alleviation of symptoms or halting the progression of the disease, as measured by a decrease in serum glucose or insulin levels in, for example, hyperinsulinemic or hyperglycemic patients.

The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

The following abbreviations are used throughout the Examples:

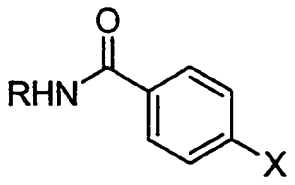
DIAD:	Diisopropyl azodicarboxylate
DIEA:	Diisopropylethylamine
DMF:	Dimethylformamide
DMAP:	4-Dimethylaminopyridine
DMSO:	Dimethylsulfoxide
EDCI:	1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride
HCl:	Hydrochloric acid
KOH:	Potassium hydroxide
LC:	Liquid Chromatography
MS:	Mass Spectroscopy
NaOH:	Sodium Hydroxide
TFA:	Trifluoroacetic acid
THF:	Tetrahydrofuran
TLC:	Thin Layer Chromatography

Example 1

Step 1. General Synthesis of Aryl Azide and Nitroaryl Intermediates.

The 4-azido or 4-nitroarylcarboxylic acid starting materials in Examples A-D of Step 1 may also be functionalized as azido or nitropyridylcarboxylic acids. These are commercially available or may be prepared by the following known methods.

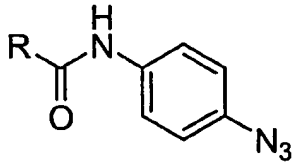
A. Carboxamides



$X = NO_2, N_3$

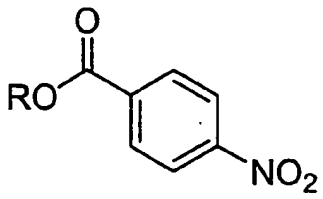
To a solution of an amine (1.0 equivalents) and 4-azido or 4-nitroarylcarboxylic acid (1.0 equivalents) in THF was added EDCI (1.5 equivalents). The mixture was stirred at room temperature for 8-12 hours. THF was removed, and the residue was resuspended in ethyl acetate, washed with water, dried over sodium sulfate, concentrated, and purified by silica gel chromatography eluting with ethyl acetate/hexane or chloroform/methanol.

B. Amides



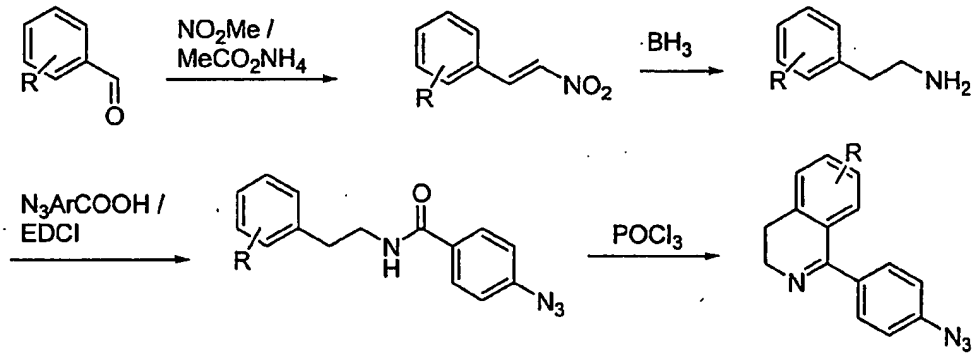
To a dry THF solution of an acid (0.5 M) and 4-azidoarylamine (1 equivalent) was added EDCI (1.5 equivalents). After stirring at room temperature for 8 hours, the reaction was concentrated *in vacuo*. The resulting mixture was diluted with ethyl acetate and washed with two portions of water. The organic layer was then isolated and dried over sodium sulfate. The solution was then filtered through a fritted funnel, concentrated, and dried overnight under high vacuum to yield the crude amidoarylazide product that was used without further purification.

C. Esters



A dry THF solution containing a 4-nitroarylcarboxylic acid (1.5 equivalents), an alcohol (1.5 equivalents), DIAD (1.5 equivalents), and PPh_3 (1.5 equivalents) was refluxed. After stirring at reflux for 2 hours, the reaction was allowed to cool to room temperature and then concentrated *in vacuo*. The resulting mixture was dissolved in methylene chloride and purified via flash chromatography. The pure fractions were combined and concentrated *in vacuo* to yield the pure nitroester product.

D. Dihydroisoquinolines



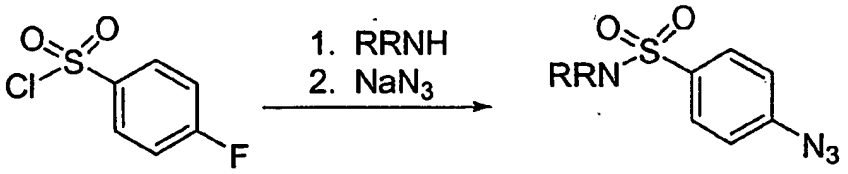
To an aryl aldehyde (1 equivalent) dissolved in acetic acid (0.66 M) was added nitromethane (3 equivalents) and ammonium acetate (1 equivalent) and the mixture was refluxed overnight. The reaction was cooled to room temperature and ethyl acetate was added. The organic phase was washed with water, $NaHCO_3$ (saturated aqueous), dried, and evaporated to yield a residue which was used without further purification.

The crude nitrostyrene product was dissolved in THF (0.2 M), was cooled to 0°C, and was treated with 1.0 M BH_3 in THF (5 equivalents). The reaction was then heated to reflux overnight. The reaction was cooled to

0°C and quenched with H_2O and then 1N HCl was added until the pH was equal to about 2. The reaction was stirred for 30 minutes at room temperature and then extracted with ether (3x). The aqueous layer was made basic with 5% NaOH solution and then extracted into ether (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel chromatography. The amine was then coupled to a 4-azido or 4-nitroarylcarboxylic acid (EDCI, THF) as described in the carboxamide synthesis above.

The resulting carboxamide was suspended in $POCl_3$, and the mixture was heated at reflux for 1-3 days. The reaction was then cooled to room temperature and cautiously poured onto ice. The aqueous mixture was washed with chloroform, and the organic layer was washed with Na_2CO_3 (saturated aqueous). The acidic aqueous phase was cooled at 0°C and made basic by addition of solid KOH. The resulting mixture was extracted with chloroform and the organic layers were combined, dried, and concentrated *in vacuo*. The resulting residue was purified on silica gel, eluting with chloroform/methanol.

E. Sulfonamides

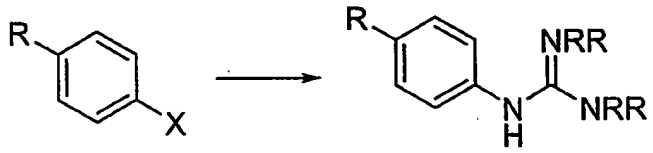


To a dry THF solution containing an amine (1.0 equivalent, 0.5 M in THF) and 4-fluorobenzenesulfonyl chloride (1.0 equivalent) was added ethyldiisopropylamine (1.1 equivalent). After stirring at room temperature for 12 hours, the reaction was concentrated *in vacuo*. The resulting mixture was diluted with ethyl acetate and washed with water (3x). The organic layer was then separated and dried over sodium sulfate. The solution was then filtered through a fritted funnel and concentrated to yield the crude product.

To a DMSO solution of the crude intermediate (1.0 equivalent, 0.5 M in DMSO) was added sodium azide (10 equivalents) and tetrabutylammonium chloride (2.3 equivalents). The reaction was fitted with a condenser and heated to 100°C for 12 hours. The reaction was then cooled to room temperature, diluted with ethyl acetate, and washed with water (3x). The organic layer was next separated, dried over sodium sulfate, filtered through cotton, concentrated, and dissolved in a minimal amount of ethyl acetate. The crude mixture was purified *via* flash chromatography using hexanes/ethyl acetate. The pure fractions were combined, concentrated, and dried overnight under high vacuum to yield the azide product.

Step 2. General Synthesis of Guanidine Products from Aryl Carboxamide, Amide, Ester, and Dihydroisoquinoline Intermediates of Step 1.

A. Preparation from Aryl Azides



$X=N_3$, NO_2

To a solution of the corresponding aryl azide (1.0 equivalent) in THF was added triphenylphosphine (1.0 equivalent) or tributylphosphine (1.0 equivalent, for use particularly with pyridylazide compounds) at room temperature. After 8 hours, the corresponding isocyanate was added (1.3 equivalents), and the solution was heated at 55-80°C overnight. To the mixture was added an amine (1.3 equivalents). After being heated at the same temperature for 2 hours, THF was removed. The residue was resuspended in ethyl acetate, washed with water, dried over anhydrous sodium sulfate, concentrated, and purified by silica gel chromatography.

B. Preparation from Nitroaryl Compounds

A nitroaryl compound was taken up in ethanol (or methanol) and purged with dry nitrogen. To this solution was introduced activated Pd/C

(10% w/w, 0.1 equivalent), and the mixture was hydrogenated for about 30 minutes or until complete by LC/MS. The mixture was then filtered through Celite, concentrated *in vacuo*, and taken on crude to the next step.

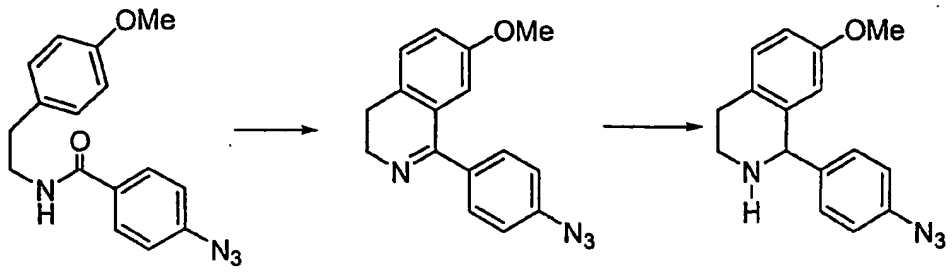
To a 0.5 M acetone solution (0°C ice bath) containing the amine (1 equivalent) and sodium carbonate (3 equivalents) was added thiophosgene (3 equivalents) dropwise. After 2 hours at room temperature, the reaction mixture was concentrated *in vacuo* to remove solvent and excess thiophosgene. The residue was taken up in ethyl acetate and washed with water, dried with sodium sulfate, and then concentrated *in vacuo* to yield the isothiocyanate. To a solution of the resulting isothiocyanate in dry THF (0.5 M solution) was added an amine (1.5 equivalents). After stirring overnight, the reaction mixture was concentrated *in vacuo* and the thiourea product was dissolved in ethyl acetate or methylene chloride and purified *via* flash chromatography.

To a solution of the thiourea in dry THF (0.1 M) was added EDC (2 equivalents) and the solution heated at reflux (~80°C external temp) for 60 minutes, after which it was cooled to room temperature and then placed in an ice bath for 15 minutes with stirring. A methylene chloride solution containing an amine (2 equivalents) was added and the reaction was stirred at room temperature. After 20 minutes, the reaction was diluted with ethyl acetate and washed with water. The aqueous layer was back extracted with ethyl acetate and the combined organic layers, after concentration *in vacuo,* was purified by silica gel flash chromatography.

Example 2

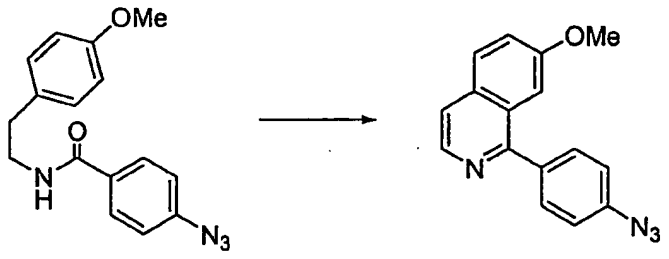
The syntheses of additional starting materials that may be used in the general procedures of Example 1 are shown and described below.

A. Preparation of 1-(4-Azido-phenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline



4-Azido-N-[2-(4-methoxy-phenyl)-ethyl]-benzamide was cyclized as described in Example 1, Step 1D. To the resulting 1-[4-(azadiazomvinyl)phenyl]-7-methoxy-3,4-dihydroisoquinoline (1 equivalent) in methanol was added paraformaldehyde (10 equivalents) and $NaCNBH_3$ (4 equivalents) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through Celite, methanol was removed in vacuo, and the residue was dissolved in chloroform and washed with water. The organic extract was dried over magnesium sulfate and evaporated *in vacuo* to give the desired intermediate as an oil, which was used without further purification.

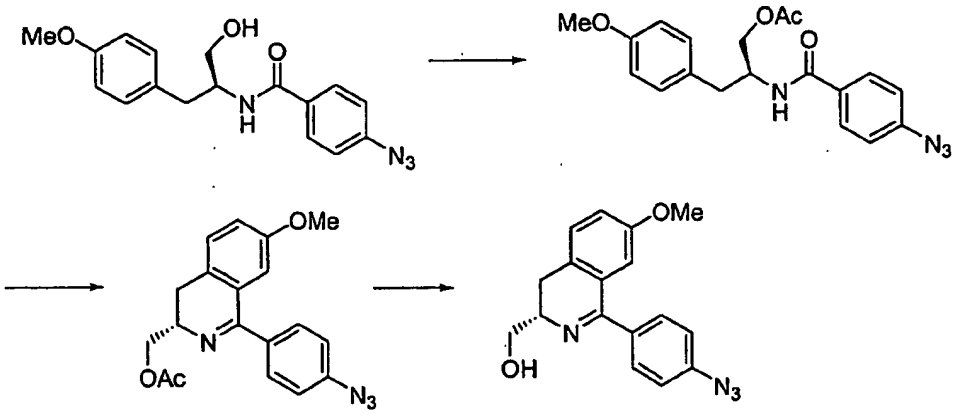
B. Preparation of 1-(4-Azido-phenyl)-7-methoxyisoquinoline



4-Azido-N-[2-(4-methoxy-phenyl)-ethyl]-benzamide was cyclized as described in Example 1, Step 1D. To a refluxing solution of 1-[4-(azadiazomvinyl)-phenyl]-7-methoxy-3,4-dihydroisoquinoline (1 equivalent) in dry benzene was added every hour activated MnO_2 (1.2 equivalent) (Dean-stark apparatus) for 8 hours, and the mixture was refluxed 24 hours. The reaction mixture was filtered through Celite, the filter cake washed with

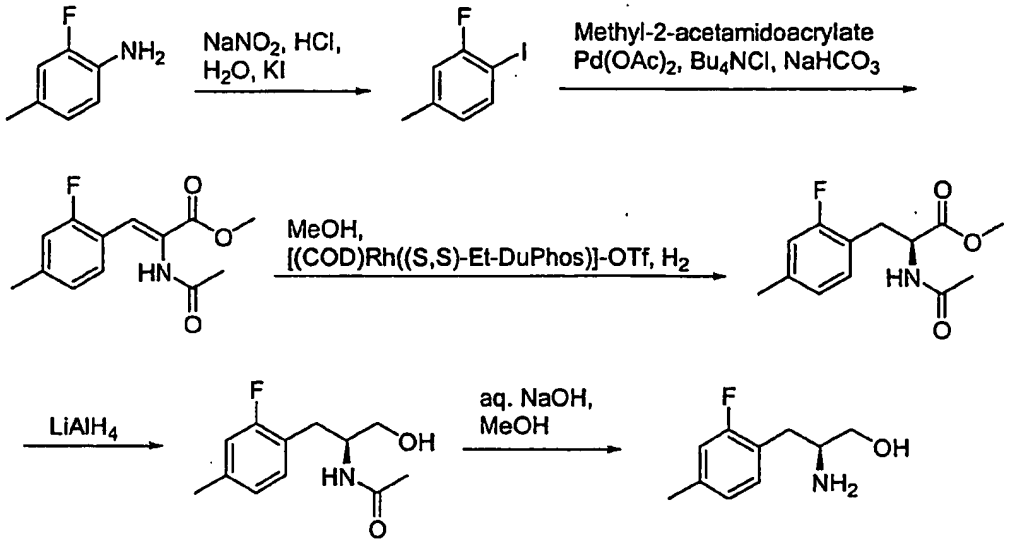
chloroform, and the filtrate evaporated in vacuo. The resulting crude product was purified on silica gel to separate the starting material, eluting with ethyl acetate/hexane 1:9 to 1:7.

C. Preparation of [1-(4-Azido-phenyl)-7-methoxy-3,4-dihydro-isoquinolin-3-yl]-methanol



The hydroxymethyl carboxamide starting material was prepared from O-methyl-L-tyrosine following the procedure described in *J. Org. Chem.*, 65, p. 503 (2000) and the coupling procedure in Example 1, Step 1A. A solution of the amide N-{(1S)-2-hydroxy-1-[(4-methoxyphenyl)methyl]ethyl}[4-(azadiazomvinyl)phenyl]-carboxamide (1 equivalent) in anhydrous pyridine and acetic anhydride (2 equivalents) was stirred at room temperature overnight. The reaction mixture was dissolved in ethyl acetate and washed with 1 M CuSO4. The organic extract was dried over magnesium sulfate and evaporated *in vacuo* to give a solid, which was used without further purification. The acetate was cyclized ($POCl_3$) as described in Example 1, step 1D. The cyclic acetate (1 equivalent) was dissolved in methanol and treated with K_2CO_3 (1 equivalent). After stirring at room temperature for 2 hours, the methanol was removed *in vacuo*, and the crude product was dissolved in chloroform and washed with water to yield [1-(4-Azido-phenyl)-7-methoxy-3,4-dihydro-isoquinolin-3-yl]-methanol.

D. Preparation of 2(S)-Amino-3-(2-fluoro-4-methyl-phenyl)-propan-1-ol



Synthesis of 2-Fluoro-1-iodo-methylbenzene

In a round bottom flask, 2-fluoro-4-methyl aniline (1 g, 7.99 mmol) was suspended in water (2 mL) and concentrated HCl (2 mL). This solution was then cooled in an ice bath with vigorous stirring. To this stirring solution was added sodium nitrite (662 mg, 9.58 mmol) dissolved in water (2 mL) dropwise over 30 minutes, keeping the temperature below 10°C. The reaction was then stirred for a further 30 minutes. The resulting solution was then added dropwise to a solution of potassium iodide (1.99 g, 11.98 mmol) dissolved in water (2 mL) stirring in an ice bath. The reaction was then refluxed for 2 hours before being allowed to stir at room temperature over night. The reaction was then taken up in ethyl acetate and washed with HCl (3 N), NaOH (1 M) containing a small portion of sodium metabisuffite. The organic layer was then dried over Na_2SO_4 and the solvent removed under reduced pressure to afford 1.46 g (77% yield) of a dark brown oil. This material was then purified via flash chromatography using a hexane running solvent and washed with 1 M HCl (2x), 2 M NaOH, brine and dried over Na_2SO_4 to recover the iodide product 829 mg (44% yield) of a colorless oil.

Synthesis of 2-Acetylamino-3-(2-fluoro-4-methyl-phenyl)-acrylic acid methyl ester via the Heck reaction

A mixture of the aryl iodide (200mg, 0.817mmol), methyl-2-acetamidoacrylate (146 mg, 1.017 mmol), $Pd(OAc)_2$, (23 mg, 0.102 mmol), tetrabutylammonium chloride hydrate (283 mg, 1.017 mmol), and sodium hydrogen carbonate (192 mg, 2.288 mmol) was weighed into a 20 mL glass vial, flushed with nitrogen and sealed. The vial was then heated at 80°C for 24 hours. The reaction was then cooled to room temperature and dissolved in methylene chloride. The organic layer was then washed with brine (3x) and dried over Na_2SO_4. The organic solvent was then removed under reduced pressure to yield a dark brown solid. This crude material was then purified via flash chromatography using 45% ethyl acetate/hexane running solvent to yield the Heck product 129 mg (60% yield) of an off white solid.

Hydrogenation to Form the 2(S)-Acetylamino-3-(2-fluoro-4-methyl-phenyl)-propionic acid methyl ester

In an oven dried Parr hydrogenation vial, the methyl ester above (129 mg, 0.51 mmol) was dissolved in anhydrous methanol (3.5 mL) along with the chiral catalyst (+)-I,2-Bis((2S,5S)-2,5-diethylphospholano)benzene (cyclooctadiene)rhodium(I) trifluoromethanesulfonate (4 mg, 5.5 μmol). The vial was then placed in the Parr pressure reactor, evacuated, and flushed with argon (5x) before evacuating and flooding with hydrogen (5x). The reaction was then allowed to proceed for 3 hours at room temperature with stirring. The reaction was then filtered through cotton wool before removing the organic solvent under reduced pressure to yield the product 100 mg (78% yield). This material was used without further purification. [M+H]+, 507.4.

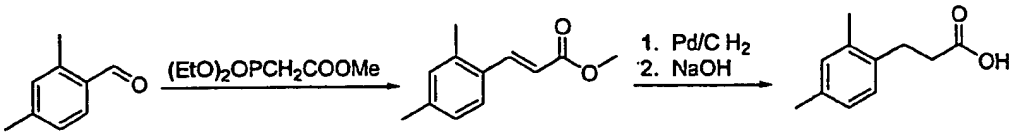
Reduction of the Methyl Ester to Form the Acetamide

In an oven dried round bottom flask under nitrogen, $LiAlH_4$ (22 mg, 0.59 mmol) was suspended in anhydrous THF (2 mL) and cooled in an ice bath. To this stirring solution was added dropwise a THF (2 mL) solution of the product (50 mg, 0. 19 mmol) from the previous step. The reaction was then allowed to warm to room temperature and monitored via TLC (45% ethyl acetate/hexane running solvent) until completion within approximately 1 hour. The reaction was then cooled in an ice bath and diluted with water and diethyl ether. To this vigorously stirring solution was added 2 M NaOH, and the reaction was then allowed to stir for a further 30 minutes. The aqueous layer was then extracted with diethyl ether (3x), and the combined organic extracts were dried over Na_2SO_4. The organic layer was then removed under reduced pressure to recover the product alcohol (35 mg, 79% yield) as an off white solid. [MH]+, 451.4.

Hydrolysis of the Acetamide to Form 2(S)-amino-3-(2-fluoro-4-methyl-phenyl)-propan-l-ol

In a round bottom flask, the acetamide from the previous step (4.748 g, 21.07 mmol) was dissolved in methanol (150 mL) and 2 M NaOH (150 mL) and refluxed. The reaction was then monitored via TLC using ethyl acetate and ninhydrin stain before it was allowed to cool to room temperature after 2 days. The reaction was then extracted with ethyl acetate (3x) and the organic layer dried over Na_2SO_4 before being removed under reduced pressure. This material was then purified via flash chromatography using a 10% methanol/methylene chloride/ 1% ammonia solution running solvent to give the amino alcohol 2.871 g (76% yield).

E. Preparation of 3-(2,4-Dimethylphenyl)-propionic acid



Synthesis of 3-(2,4-Dimethylphenyl)-acrylic acid methyl ester

In an oven dried round bottom flask under nitrogen, 2,4-dimethylbenzaldehyde (10 g, 74.52 mmol) and sodium hydride (3.28 g, 81.89 mmol) were suspended in anhydrous DMF (100 mL) and stirred in an ice bath. To this stirring solution was added dropwise methyl diethyl(phosphonoacetate) (15 mL, 81.98 mmol), and the solution was allowed to stir for a further 15 minutes before being allowed to warm to room temperature and proceed for two days. The reaction was then taken up in ethyl acetate and washed with 1 M HC1 (2x) and brine. The organic layer was then dried over sodium sulfate and the solvent removed under reduced pressure to recover the desired product 16.45 g. This material was used without further purification.

Hydrogenation to Yield 3-(2,4-Dimethylphenyl)-propionic acid methyl ester

3-(2,4-dimethylphenyl)-acrylic acid methyl ester (16.45 g, 86.44 mmol) was dissolved in methanol (120 mL) and evacuated (3x) connected to a hydrogenation apparatus. 10% Pd on C (1.0 g) was added to the flask under nitrogen, and the reaction was evacuated again. The vigorously stirring solution was then allowed to proceed under H_2 and monitored via NMR until the reaction was complete. After two days, the reaction was filtered through a Celite pad and concentrated to afford 3-(2,4-dimethylphenyl)-propionic acid methyl ester 15.1 g (90% yield). 193.1 [M+H]+.

Hydrolysis to yield 3-(2,4-Dimethylphenyl)-propionic acid

3-(2,4-dimethylphenyl)-propionic acid methyl ester (15.1 g, 78.54 mmol) was heated to reflux in 2.0 M NaOH (150 mL) overnight. The reaction was cooled, and washed with diethyl ether (2x) and the aqueous

layer acidified with 2 N HCl to precipitate the desired 3-(2,4-dimethylphenyl)-propionic acid. The precipitate was collected by filtration and dried under vacuum (9.12 g, 68% yield).

Example 3

Preparation of (3S)-N'-[4-(3,4-Dihydroquinolin-1(2H)-ylcarbonyl)phenyl]-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide

Step 1. Preparation of 1-[(4-Azidophenyl)carbonyl]-1,2,3,4-tetrahydroquinoline

A mixture of 1,2,3,4-tetrahydro-quinoline, 4-azidobenzoic acid, and 1-[3-(dimethlamino)propyl]-3-ethylcarbodiimide hydrochloride (1:1:1.5) were stirred in THF (0.43 M amine) for 20 hours at room temperature. After decanting and washing any remaining insoluble material with THF, the THF was removed *in vacuo*. The resulting solid was recrystallized from boiling ethyl acetate.

Step 2. Preparation of (3S)-N'-[4-(3,4-Dihydroquinolin-1(2H)-ylcarbonyl)phenyl]-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide

To a solution of 1-[(4-azidophenyl)carbonyl]-1,2,3,4-tetrahydroquinoline (1 equivalent; 0.1 M in anhydrous THF) was added trimethylphosphine (1 equivalent; 1 M in THF). After stirring for 10 minutes, (1S,2S,3S,5S)-2,6,6-trimethyl-bicyclo[3.1.1]heptan-3-isocyanate (1.3 equivalents) was added. After stirring at 55°C for 18 hours, (S)-(+)-2-methylpiperazine (1.6 equivalents) was added, and the reaction was stirred at 55°C for an additional 2 hours. Volatiles were removed *in vacuo* and the resulting off-white solid was run through a preparatory LC. Lyophilization of the pure fractions resulted in a fluffy white powder.

Example 4

Preparation of (3S)-3-Methyl-N'-(4-{[7-(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide

Step 1. Preparation of 4-Azido-*N*-{2-[4-(methyloxy)phenyl]ethyl}benzamide

A mixture of 2-(4-methoxy-phenyl)-ethylamine, 4-azidobenzoic acid, and 1-[3-(dimethlamino)propyl]-3-ethylcarbodiimide hydrochloride (1:1:1.5) were stirred in THF (0.43 M amine) for 20 hours at room temperature. After decanting and washing any remaining insoluble material with THF, the THF was removed *in vacuo*. The resulting solid was recrystallized from boiling ethyl acetate.

Step 2. Preparation of 2-[(4-Azidophenyl)carbonyl]-7-(methyloxy)-1,2,3,4-tetrahydroisoquinoline

To a mixture of 4-azido-*N*-{2-[4-(methyloxy)phenyl]ethyl}benzamide and paraformaldahyde (1:1.1) was added formic acid (0.35 M in benzamide). After stirring for 18 hours at 55°C, ethyl acetate was added, and the reaction was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic fraction was dried with $MgSO_4$, followed by removal of ethyl acetate *in vacuo*. Purification by flash chromatography, eluting with 30% ethyl acetate in hexanes resulted in a white solid.

Step 3. Preparation of (3S)-3-Methyl-N'-(4-{[7-(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide

To a solution of 2-[(4-azidophenyl)carbonyl]-7-(methyloxy)-1,2,3,4-tetrahydroisoquinoline (1 equivalent; 0.1 M in anhydrous THF) was added trimethylphosphine (1 equivalent; 1 M in THF). After stirring for 10 minutes, (1S,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-isocyanate (1.3 equivalents) was added. After stirring at 55°C for 18 hours, (S)-(+)-2-

methylpiperazine (1.6 equivalents) was added, and the reaction was stirred at 55°C for an additional 2 hours. Volatiles were removed *in vacuo*, and the resulting off-white solid was run through a preparatory LC. Lyophilization of the pure fractions resulted in a fluffy white powder.

Examples 5-23

The compounds in the following table were prepared using the methodology described in Examples 3 and 4. The starting materials used in the syntheses are recognizable to one of skill in the art and are commercially available or may be prepared using known methods.

Table of Examples 5-23

Example	Name	MH+
5	(3S)-N'-{4-[(5,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]phenyl}-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	542.8
6	(3S)-3-methyl-N'-(4-{[6-(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	544.7
7	(3S)-N-[4-(2,3-dihydro-1H-indol-1-ylcarbonyl)phenyl]-3-methyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	500
8	(3S)-N'-{5-[(7-bromo-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]pyridin-2-yl}-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	593.6
9	(3S)-N'-{5-[(7-chloro-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]pyridin-2-yl}-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	549.2

10	(3S)-N'-{5-[(7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]pyridin-2-yl}-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	533.3
11	(3S)-N-cycloheptyl-3-methyl-N'-(4-{[7-(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)piperazine-1-carboximidamide	504.2
12	(3S)-3-methyl-N-(4-methylcyclohexyl)-N'-(4-{[6-(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)piperazine-1-carboximidamide	504.5
13	(3S)-N'-(4-{[6,7-bis(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-3-methyl-N-[(1R,2S,3S,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	574.5
14	(3S)-3-methyl-N-(4-methylcyclohexyl)-N'-(4-{[7-(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)piperazine-1-carboximidamide	504.5
15	(3S)-N-cycloheptyl-3-methyl-N'-(4-{[6-(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)piperazine-1-carboximidamide	504.6
16	(3S)-N'-{4-[(5,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]phenyl}-3-methyl-N-(4-methylcyclohexyl)piperazine-1-carboximidamide	502.5
17	(3S)-N-cycloheptyl-N'-{4-[(5,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]phenyl}-3-methylpiperazine-1-carboximidamide	502.5
18	(3S)-N'-(4-{[6,7-bis(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-N-cycloheptyl-3-methylpiperazine-1-carboximidamide	534.5
19	(3S)-N'-(4-{[6,7-bis(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}phenyl)-3-methyl-N-(4-methylcyclohexyl)piperazine-1-carboximidamide	534.3

20	(3S)-N-{4-[(7-bromo-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]phenyl}-3-methyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	592.2
21	(3S)-N-{4-[(7-chloro-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]phenyl}-3-methyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	548.2
22	(3S)-N-{4-[(7-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)carbonyl]phenyl}-3-methyl-N'-[(1S,2S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	532
23	(3S)-3-methyl-N-(5-{[7-(methyloxy)-3,4-dihydroisoquinolin-2(1H)-yl]carbonyl}pyridin-2-yl)-N'-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	545

Example 24

Preparation of (3S)-3-methyl-N-(4-{[7-(methyloxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]carbonyl}phenyl)-N'-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide

Step 1.

2-(3-methoxy-phenyl)-ethylamine (1 equivalent) was dissolved in anhydrous methylene chloride (0.88 M) in a three necked round bottom flask under N_2 and stirred in an ice bath. Tosyl chloride (1.25 equivalent) was then dissolved in anhydrous methylene chloride under N_2 and added to this stirring solution over 10 minutes (Caution! This is an exothermic reaction). A precipitate formed, DIEA (1.2 equivalent) was then added, and the reaction was stirred at room temperature overnight. The reaction was then washed with 10% citric acid, 10% sodium carbonate, and brine before being dried over sodium sulfate. The organic solvent was then removed under reduced pressure to provide a brown oil. This crude material was then purified via

flash chromatography using 100% methylene chloride running solvent to recover the product sulfonamide. (MH+) 306.1.

Step 2.

The sulfonamide (1 equivalent) produced in Step 1 was dissolved in acetone and stirred in a round bottom flask with K_2CO_3 (6.9 equivalents). The mixture was warmed to 78°C and refluxed. Ethyl bromoacetate (1.5 equivalents) was then added, and the reaction was allowed to proceed overnight. The K_2CO_3 was then filtered off, and the solvent was removed under reduced pressure. To this colorless oil was added NaOH (4.4 equivalents) dissolved in 50% ethanol (0.4 M). The mixture was then warmed to reflux at 90°C and allowed to proceed overnight. The ethanol was then removed under reduced pressure. The residual oil was then washed with water and extracted with diethyl ether. The aqueous layer was then acidified with concentrated HCl and extracted with diethyl ether (2x). The organic layers were then combined and extracted with sodium carbonate (2x). The aqueous layers were then combined and acidified with concentrated HCl and extracted with diethyl ether (2x). The organic layers were then combined and dried over sodium sulfate. The organic solvent was then removed under reduced pressure. The resulting material was then recrystallized from ethyl acetate/petroleum spirit to recover the alkylated product [[2-(3-methoxy-phenyl)-ethyl]-(toluene-4-sulfonyl)-amino]-acetic acid. (MH+) 363.9.

Step 3.

[[2-(3-Methoxy-phenyl)-ethyl]-(toluene-4-sulfonyl)-amino]-acetic acid (1 equivalent) was dissolved in anhydrous methylene chloride (0.13 M) and added to a stirring solution of P_2O_5 (5 equivalents) suspended in anhydrous methylene chloride (0.13 M) at 0°C under nitrogen. The reaction was then allowed to proceed at room temperature for two days before being worked up. The reaction mixture was then diluted with 3% NaOH and extracted with methylene chloride. The organic layers were then combined and dried over sodium sulfate, and the solvent was removed under reduced

pressure to recover the cyclized product 8-methoxy-3-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[d]azepin-1-one. The regio-isomer (ortho cyclized product) is formed in this reaction. The resulting material was purified via flash chromatography using 20% acetone/petroleum spirit running solvent. Two separate fractions of the desired isomeric pure 8-methoxy-3-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-benzo[d]azepin-1-one were recovered. These two fractions were treated separately for the next reaction. (MH+) 346.1.

Step 4.

The ketone product from Step 3 was dissolved in neat TFA and stirred under nitrogen. To this stirring solution was added triethyl silane (2.2 equivalents), and the reaction was allowed to proceed overnight at room temperature. Aqueous sodium carbonate was then added, and the solution was extracted with ether (2x). The ether layers were then combined and dried over sodium sulfate, and the solvent was removed under reduced pressure to recover an orange oil. The crude material from the two reactions was then combined and purified via flash chromatography using 20% acetone/1% ammonia solution/petroleum spirit to give 7-methoxy-3-(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine. (MH+) 178.0.

Step 5.

Gaseous ammonia was first condensed into an oven dried three necked round bottom flask in a dry ice acetone bath under N_2. Sodium metal was then added to this vigorously stirring liquid ammonia to form sodium amide. The solution should hold a deep blue color to confirm that the liquid ammonia is anhydrous. The sulfonamide (1 equivalent) from Step 4 was then dissolved in THF (0.1 M) in an oven dried round bottom flask connected to a dry ice condenser. The anhydrous liquid ammonia was then distilled across into the round bottom flask containing the sulfonamide with vigorous stirring via the dry ice condenser connected in a series under a steady stream of N_2. Once the distillation had finished, the condenser and round bottom flask containing the sulfonamide was isolated. Sodium metal (2.1 equivalents) was

then added until the solution again became a deep blue color. The reaction was stirred for a further 30 minutes before being quenched with NH_4Cl (9.3 equivalents). The reaction was then extracted with diethyl ether and dried over sodium sulfate, and the solvent was removed under reduced pressure to give the product amine as a yellow oil. (MH+) 353.3.

Step 6.

7-Methoxy-2,3,4,5-tetrahydro-1H-benzo[d]azepine (1 equivalent) was dissolved in THF (0.1 M) along with azidobenzoic acid (1.5 equivalents), EDCI (1.5 equivalents), DMAP (0.18 equivalents), and DIEA (1.5 equivalents). The reaction was stirred at room temperature overnight. The reaction was then washed with 10% citric acid, saturated sodium carbonate, and brine. The organic layer was then dried over sodium sulfate, and the organic solvent was removed under reduced pressure. The material was then purified via flash chromatography using 8% acetone/1% ammonia solution/petroleum spirit running solvent to give (4-azido-phenyl)-(7-methoxy-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl)-methanone. (MH+) 323.2.

Step 7.

(3S)-3-methyl-N-(4-{[7-(methyloxy)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]carbonyl}phenyl)-N'-[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide was prepared using the product of Step 6 and following the procedure in Example 3. (MH+) 558.8.

Examples 25-45

The compounds in the following table were prepared using the methodology described in Examples 1 and 2. The starting materials used in the syntheses are recognizable to one of skill in the art and are commercially available or may be prepared using known methods.

Table of Examples 25-45

Example	Name	MH+
25	(3S)-3-methyl-N-{4-[7-(methyloxy)-3,4-dihydroisoquinolin-1-yl]phenyl}-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	514
26	(3S)-3-methyl-N-[4-(7-methyl-3,4-dihydroisoquinolin-1-yl)phenyl]-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	498
27	(3S)-3-methyl-N-{4-[7-(methyloxy)-1,2,3,4-tetrahydroisoquinolin-1-yl]phenyl}-N'-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	516
28	(3S)-N-{4-[6,7-bis(methyloxy)-3,4-dihydroisoquinolin-1-yl]phenyl}-3-methyl-N'-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	544
29	(3S)-3-methyl-N-{4-[6-(methyloxy)-3,4-dihydroisoquinolin-1-yl]phenyl}-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	514
30	(3S)-3-methyl-N-{4-[2-methyl-7-(methyloxy)-1,2,3,4-tetrahydroisoquinolin-1-yl]phenyl}-N'-[(1S,2S,3R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	530
31	(3S)-N-[4-(3,4-dihydrobenzo[h]isoquinolin-1-yl)phenyl]-3-methyl-N'-[(1S,2S,3R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	534
32	(3S)-3-methyl-N-(4-{7-[(1-methylethyl)oxy]-3,4-dihydroisoquinolin-1-yl}phenyl)-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	542

33	(3S)-3-methyl-N-{4-[7-(methyloxy)isoquinolin-1-yl]phenyl}-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	512
34	(3S)-3-methyl-N-{4-[7-(1-methylethyl)-3,4-dihydroisoquinolin-1-yl]phenyl}-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	526
35	(3S)-N-{4-[7-(ethyloxy)-3,4-dihydroisoquinolin-1-yl]phenyl}-3-methyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	528
36	(3S)-N-{4-[(3S)-3-(hydroxymethyl)-7-(methyloxy)-3,4-dihydroisoquinolin-1-yl]phenyl}-3-methyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	544
37	(3S)-3-methyl-N-{5-[7-(methyloxy)-3,4-dihydroisoquinolin-1-yl]pyridin-2-yl}-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	515
38	(3S)-N-{5-[7-(ethyloxy)-3,4-dihydroisoquinolin-1-yl]pyridin-2-yl}-3-methyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	529
39	(3S)-N-{4-[7-(butyloxy)-3,4-dihydroisoquinolin-1-yl]phenyl}-3-methyl-N'-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	556
40	(3R,5S)-N-{4-[7-(butyloxy)-3,4-dihydroisoquinolin-1-yl]phenyl}-3,5-dimethyl-N'-[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	570
41	(3S)-N-{5-[7-(1,1-dimethylethyl)-3,4-dihydroisoquinolin-1-yl]pyridin-2-yl}-3-methyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	542

42	(3R,5S)-N-{5-[7-(ethyloxy)-3,4-dihydroisoquinolin-1-yl]pyridin-2-yl}-3,5-dimethyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	543
43	(3R,5S)-3,5-dimethyl-N-{5-[7-(1-methylethyl)-3,4-dihydroisoquinolin-1-yl]pyridin-2-yl}-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	541
44	(3S)-N-{5-[7-(1,1-dimethylethyl)-3,4-dihydroisoquinolin-1-yl]pyridin-2-yl}-3-methyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	541
45	(3S,5S)-N-{5-[7-(ethyloxy)-3,4-dihydroisoquinolin-1-yl]pyridin-2-yl}-3,5-dimethyl-N'-[(1S,2S,3R,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	544

Examples 46-76

The compounds in the following table were prepared using the methodology described in Examples 1 and 2. The starting materials used in the syntheses are recognizable to one of skill in the art and are commercially available or may be prepared using known methods.

Table of Examples 46-76

Example	Name	MH+
46	2-(2,4-dichlorophenyl)ethyl 4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]benzoate	571.2
47	2-(2,4-dichlorophenyl)ethyl 4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]benzoate	585.2

48	2-(2,4-dichlorophenyl)ethyl 4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[4-(trifluoromethyl)cyclohexyl]imino}methyl)amino]benzoate	585.1
49	4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]benzoic acid	413.2
50	4-chloro-N-{4-[((E)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-D-phenylalaninamide	551.3
51	ethyl 4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]benzoate	441.3
52	3-[2-fluoro-4-(methyloxy)phenyl]-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	550.3
53	3-(2,4-dimethylphenyl)-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	530.3
54	3-(2-fluoro-4-methylphenyl)-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	534.3
55	2,4-dichloro-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-L-phenylalaninamide	585.2
56	2,4-dichloro-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-D-phenylalaninamide	585.2
57	2,4-dichloro-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-D-phenylalaninamide	599.3

58	N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[4-(methyloxy)phenyl]propanamide	546.3
59	N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]propanamide	564.3
60	N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-(2-fluoro-4-methylphenyl)propanamide	548.3
61	3-[2,4-bis(methyloxy)phenyl]-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	576.3
62	N-acetyl-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-fluoro-4-methyl-D-phenylalaninamide	605.4
63	N-acetyl-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-fluoro-O-methyl-D-tyrosinamide	621.3
64	N-acetyl-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-fluoro-O-methyl-L-tyrosinamide	621.3
65	N^2-acetyl-3-(1,3-benzodioxol-4-yl)-N^1-{4-[((Z)-[(3*R*,5*S*)-3,5-dimethylpiperazin-1-yl]-{[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-D-alaninamide	617.3
66	N-acetyl-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2,4-difluoro-D-phenylalaninamide	609.3

67	N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-fluoro-O-methyl-D-tyrosinamide	603.3
68	N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-fluoro-4-methyl-D-phenylalaninamide	563.4
69	N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-fluoro-O-methyl-D-tyrosinamide	579.3
70	N-{4-[((Z)-[(3S,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-(2-fluoro-4-methylphenyl)propanamide	548.3
71	N-{4-[((Z)-[(3S,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]propanamide	564.3
72	(3S)-N-[4-({[2-(2,4-dichlorophenyl)ethyl]amino}sulfonyl)phenyl]-3-methyl-N'-(2-methylcyclohexyl)piperazine-1-carboximidamide	566.1
73	(3S)-N'-cyclohexyl-N-[4-({[2-(2,4-dichlorophenyl)ethyl]amino}sulfonyl)phenyl]-3-methylpiperazine-1-carboximidamide	552.1
74	(3S)-N-[4-({[2-(2,4-dichlorophenyl)ethyl]amino}sulfonyl)phenyl]-3-methyl-N'-(4-methylcyclohexyl)piperazine-1-carboximidamide	566
75	(3*S*)-*N*-[4-({[2-(2,4-dichlorophenyl)ethyl]amino}-sulfonyl)phenyl]-3-methyl-*N*-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]piperazine-1-carboximidamide	--
76	(3*S*)-*N*-[4-({[2-(2,4-dichlorophenyl)ethyl]amino}-sulfonyl)phenyl]-3-methyl-*N*'-spiro[2.5]oct-4-ylpiperazine-1-carboximidamide	--

Examples 77-135

The compounds in the following table were prepared using the methodology described in Examples 1 and 2. The starting materials used in the syntheses are recognizable to one of skill in the art and are commercially available or may be prepared using known methods. These compounds were named using using ACD Name version 5.07 software (November 14, 2001) available from Advanced Chemistry Development, Inc.

Table of Examples 77-135

Example	Name	MH+
77	(2S)-N-{4-[(Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]-2-{[(phenylmethyl)oxy]methyl}propanamide	684.9
78	(2R)-2-amino-3-(2,4-dichlorophenyl)-N-{4-[(Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	586.6
79	(2S)-2-amino-3-(2,4-dichlorophenyl)-N-{4-[(Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	586.6
80	3-(4-bromo-2-fluorophenyl)-N-{4-[(Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	599.6
81	(2R)-2-amino-3-(2,4-dichlorophenyl)-N-{4-[(Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	586.6
82	3-[2,4-bis(methyloxy)phenyl]-N-{4-[(Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	562.8

83	1,1-dimethylethyl (1R)-1-[(4-chlorophenyl)methyl]-2-({4-[((E)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}amino)-2-oxoethylcarbamate	652.3
84	3-(4-bromo-2-fluorophenyl)-N-{4-[((E)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	613.6
85	3-(4-bromo-2-fluorophenyl)-N-{4-[((E)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	613.6
86	(2R)-2-amino-3-(4-chlorophenyl)-N-{4-[((E)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	552.2
87	(2R)-2-amino-3-(2,4-dichlorophenyl)-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	586.6
88	3-(2,4-dichlorophenyl)-N-{4-[((E)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	571.6
89	3-(2,4-difluorophenyl)-N-{4-[((E)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	538.7
90	3-(2,4-dimethylphenyl)-N-{4-[((E)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	544.8
91	3-(2,4-dimethylphenyl)-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	530.8

92	3-(2,4-dichlorophenyl)-N-[4-({(E)-[(4-methylcyclohexyl)imino][(3S)-3-methylpiperazin-1-yl]methyl}amino)phenyl]propanamide	531.5
93	(2R)-2-amino-3-(2,4-dichlorophenyl)-N-{4-[(Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	586.6
94	(2R)-2-amino-3-(2,4-dichlorophenyl)-N-{4-[(Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	586.6
95	N-[4-({(Z)-(cyclohexylimino)[(3S)-3-methylpiperazin-1-yl]methyl}amino)phenyl]-3-(2,4-dichlorophenyl)propanamide	517.5
96	(3R)-3-amino-N-{4-[(Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-phenylpropanamide	517.7
97	(2R)-2-amino-3-(2,4-dichlorophenyl)-N-{4-[(Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	600.6
98	(3R)-N-{4-[(Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	543.8
99	(2R)-2-(acetylamino)-N-{4-[(Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-(2-fluoro-4-methylphenyl)propanamide	605.8
100	(2S)-2-amino-3-(2,4-dichlorophenyl)-N-{4-[(Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	600.6

101	(2R)-2-(acetylamino)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]propanamide	621.8
102	(2S)-2-(acetylamino)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]propanamide	621.8
103	(2R)-2-(acetylamino)-3-(1,3-benzodioxol-4-yl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	617.8
104	(2R)-2-(acetylamino)-3-(2,4-difluorophenyl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	609.8
105	(2R)-2-(acetylamino)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[3-(methyloxy)phenyl]propanamide	603.8
106	(2R)-2-amino-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-(2-fluoro-4-methylphenyl)propanamide	563.8
107	(2R)-2-amino-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]propanamide	579.8
108	(2R)-2-(acetylamino)-3-(1,3-benzodioxol-5-yl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	617.8

109	(2S)-2-(acetylamino)-3-(1,3-benzodioxol-4-yl)-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	603.8
110	(2S)-2-(acetylamino)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[3-(methyloxy)phenyl]propanamide	603.8
111	(2S)-2-(acetylamino)-3-(2,4-difluorophenyl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	609.8
112	1,1-dimethylethyl (1R)-2-({4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}amino)-1-(naphthalen-1-ylmethyl)-2-oxoethylcarbamate	681.9
113	1,1-dimethylethyl (1R)-2-({4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}amino)-1-(naphthalen-2-ylmethyl)-2-oxoethylcarbamate	681.9
114	(2R)-2-amino-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-naphthalen-1-ylpropanamide	581.8
115	(2R)-2-amino-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-naphthalen-2-ylpropanamide	581.8
116	3-[2-fluoro-4-(methyloxy)phenyl]-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[4-(trifluoromethyl)cyclohexyl]imino}methyl)amino]phenyl}propanamide	564.6

117	(2R)-2-amino-3-[2-fluoro-4-(methyloxy)phenyl]-N-{4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	565.7
118	(2R)-2-(acetylamino)-3-(4-bromo-2-fluorophenyl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	670.7
119	(3R)-N-[(1R)-1-[(4-chlorophenyl)methyl]-2-({4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}amino)-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	725.4
120	(3R)-N-[(1R)-1-[(4-chlorophenyl)methyl]-2-({4-[((Z)-[(3S)-3-methylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}amino)-2-oxoethyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	711.4
121	(2S)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]-2-{[(phenylmethyl)oxy]methyl}propanamide	684.9
122	(2S)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]-2-(hydroxymethyl)propanamide	594.8
123	(2R)-2-(acetylamino)-3-(2,4-dimethylphenyl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	601.8
124	phenylmethyl (1R)-2-({4-[((Z)-[(3S,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}amino)-1-{[2-fluoro-4-(methyloxy)phenyl]methyl}-2-oxoethyl(methyl)carbamate	727.9

125	(2R)-2-(acetylamino)-3-(2,4-dimethylphenyl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}propanamide	601.8
126	(2S)-3-(2,4-dimethylphenyl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-(hydroxymethyl)propanamide	574.8
127	(2S)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-(4-fluoro-2-methylphenyl)-2-(hydroxymethyl)propanamide	578.8
128	(2S)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-(2-fluoro-4-methylphenyl)-2-{[(phenylmethyl)oxy]methyl}propanamide	668.9
129	(2S)-3-(2,4-dimethylphenyl)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-{[(phenylmethyl)oxy]methyl}propanamide	664.9
130	(2S)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-(2-fluoro-4-methylphenyl)-2-(hydroxymethyl)propanamide	578.8
131	(2R)-N-{4-[((Z)-[(3S,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]-2-(methylamino)propanamide	593.8
132	(2S)-3-{[(3-bromophenyl)methyl]oxy}-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-{[2-fluoro-4-(methyloxy)phenyl]methyl}propanamide	763.8

133	(2S)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]-2-({[(4-methylphenyl)methyl]oxy}methyl)propanamide	698.9
134	(2S)-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-3-[2-fluoro-4-(methyloxy)phenyl]-2-({[(4-fluorophenyl)methyl]oxy}methyl)propanamide	702.9
135	(2S)-3-{[(4-chloro-2-fluorophenyl)methyl]oxy}-N-{4-[((Z)-[(3R,5S)-3,5-dimethylpiperazin-1-yl]{[(1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]imino}methyl)amino]phenyl}-2-{[2-fluoro-4-(methyloxy)phenyl]methyl}propanamide	737.3

EC_{50} values of test compounds were determined by treating cells expressing MC4-R with test compound and lysing the cells and measuring intercellular cAMP concentration with an Amersham-Pharmacia RPA-559 cAMP Scintillation Proximity Assay (SPA) kit. The compounds described above were synthesized and tested according to this assay. Each of the named compounds of Examples 3-135 were found or will be found to exhibit MC4-R agonist activity and thus is useful in treating MC4-R mediated conditions. Additionally, Examples 3-95, 97, 99-102, 106, 107, 121, 126, 128-130, and 132-135 exhibited -log EC_{50} values above about 3. For these reasons, each of the exemplary compounds are individually preferred and are preferred as a group. Furthermore, the groups corresponding to R^1 through R^{19}, $R^{1'}$ through $R^{4'}$, Q, W, X, Y, and Z, and the values of m and n for each of the named compounds of Examples 3-135 are also preferred. Nomenclature for these compounds was provided using ACD/namebatch version 4.53 software available from Advanced Chemistry Development, Inc. and ACD Name version 5.07 software (November 14, 2001) available from Advanced Chemistry Development, Inc. Some of the starting materials were named using standard IUPAC nomenclature and ChemDraw AutoNom version 2.1.

Example compounds 3-135 are illustrative and should not be construed as limiting of the instant invention.

In Vivo Studies of MC4-R Agonists on Energy Intake, Body Weight, Hyperinsulinemia, and Glucose Levels

In vivo studies are conducted to observe the effect of MCR-4 agonists on energy intake, body weight, hyperinsulinemia, and glucose levels. All studies are conducted with male 9-10 week old ob/ob mice which display early onset of obesity, insulin resistance and diabetes due to leptin deficiency. Mice are acclimated in the facility for 1 week before studies and are caged individually. Vehicle-treated (control) and drug treated mice studies are always run in parallel. In multi-day studies, mice (8-15 per group) are monitored for baseline body weight, fasting levels of glucose, insulin, blood lipids and energy expenditure and then injected twice daily (9 a.m. and 5 p.m.) with 3 mg/kg of a MC4-R agonist of the present invention for 4 weeks. Body weight as well as food and water intake are monitored daily. Animals are fasted overnight for measurements of fasting levels of glucose, insulin, and lipids once a week until the end of the study. Energy expenditure (resting metabolic rate, i.e., O_2 consumption and CO_2 production) are monitored in air tight chambers at the end of the study on fed animals. O_2 consumption and CO_2 production are measured using Oxymax systems (Columbus Instruments). Oral glucose tolerance test (OGTT – a routine test for diabetes and glucose intolerance) is performed on overnight fasted mice at the end of the study. Blood glucose and oral glucose tolerance are measured using a glucose monitor (Onetouch sold by Lifescan). Free fatty acids are measured using an non-esterified free fatty acids enzymatic assay (Waco Chemicals). Serum Insulin levels are measured by immunoassay (Alpco).

Results

The effect of the compounds of the present invention on food intake is determined by measuring grams/mouse/day throughout a 4 week

study. Food is monitored every morning. Cumulative food intake represents the total amount of grams the mice consume during the study. A significant reduction in food intake is demonstrated in those mice treated IP with the compounds of the present invention.

The effect of the compounds of the present invention on body weight is determined by measuring grams/mouse throughout a 4 week study. Mice are weighed every morning. A significant body weight reduction is demonstrated in those mice treated IP with the compounds of the present invention.

The effect of the compounds of the present invention on blood glucose levels is determined by measuring blood glucose levels as represented as mg of glucose/dL of blood. Mice are fasted overnight and glucose levels are measured the following morning. Vehicle treated mice show an increase in blood glucose consistent with the rapid progression of diabetes in this mouse strain whereas, diabetes is slowed down considerably in drug treated mice. A significant reduction in fasting glucose levels is demonstrated in those mice treated IP with the compounds of this invention.

The effect of the compounds of the present invention on glucose levels during oral glucose tolerance test (OGTT) is determined by measuring blood glucose in overnight fasted mice. Blood glucose is represented as mg of glucose/dL of blood. Glucose levels are measured the following morning. Orally administered glucose quickly elevates blood glucose, similar to a meal, and the response to this exogenous glucose gives a measure of how well the body regulated glucose homeostasis. Vehicle treated mice show an elevated response to glucose consistent with their diabetic state, whereas drug treated mice show a very much improved glucose disposal.

The effect of the compounds of the present invention on free fatty acid (FFA) levels is determined by measuring mmoles of FFA/L of serum. Mice are fasted overnight and free fatty acid levels are measured the following

morning. Vehicle treated mice show elevated levels of FFA throughout the study consistent with their obese state, whereas the drug treated mice diabetes show a dramatic decrease.

The effect of the compounds of the present invention on serum insulin levels is determined by measuring serum insulin levels one hour after single IP dosing of I and 3 mg/kg in overnight fasted ob/ob mice. Serum insulin levels are represented as ng of insulin/mL of serum. Drug treated mice show a dose dependent decrease relative to vehicle.

It is understood that the invention is not limited to the embodiments specifically set forth herein for illustration, but embraces all such forms thereof as would be understood by one of skill in the art and come within the scope of the following claims.

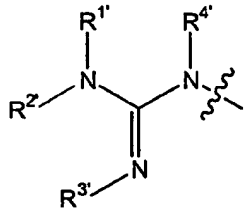
CLAIMS

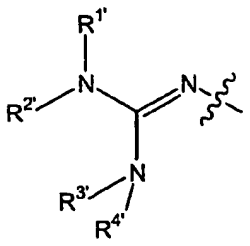
What is claimed is:

1. A compound of formula A^1-A^2-A^3-A^4

wherein

A^1 is a group of formula IIA or IIB;





IIA IIB

$R^{1'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

$R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

or $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl or heteroaryl group;

$R^{3'}$ is selected from the group consisting of substituted and unsubstituted aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

$R^{4'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, and heteroarylalkyl groups;

A^2 is selected from the group consisting of substituted and unsubstituted aryl groups and substituted and unsubstituted heteroaryl groups;

A^3 is a covalent bond such that A^2 is directly bonded to A^4, or A^3 is a linking group selected from the group consisting of O, S, $-NR^a-$, $-C(=O)-$, $-C(=O)O-$, $-NR^aC(=O)-$, $-SO_2NR^a-$, $-C(=S)-$, $-C(=O)S-$, $-P(=O)R^b-$, $-SO_2-$, and $-S(=O)-$, wherein if A^3 is a linking group, then it is bonded to A^2 and A^4 in a configuration selected from the group consisting of A^2-O-A^4, A^2-S-A^4, A^2-NR^a-A^4, A^2-C(=O)-A^4, A^2-C(=O)O-A^4, A^4-C(=O)O-A^2, A^2-NR^aC(=O)-A^4, A^4-NR^aC(=O)-A^2, A^2-SO_2NR^a-A^4, A^4-SO_2NR^a-A^2, A^2-C(=S)-A^4, A^2-(C=O)S-A^4, A^4-(C=O)S-A^2, A^2-(P=O)R^b-A^4, A^2-SO_2-A^4, and A^2-S(=O)-A^4 provided that if A^3 is a linking group with the configuration A^4-NR^aC(=O)-A^2, then A^2 is not a substituted or unsubstituted phenyl group and is not a substituted or unsubstituted 6-membered N-containing heteroaryl group;

A^4 is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups;

R^a is selected from the group consisting of H, and substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups;

R^b is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups; and

prodrugs thereof, pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, hydrates thereof, hydrides thereof, or solvates thereof.

2. The compound of claim 1, wherein A^2 is selected from the group consisting of substituted and unsubstituted phenyl groups and substituted and unsubstituted pyridyl groups.

3. The compound of claim 1, wherein A^3 is a linking group bonded to A^2 and A^4 in a configuration selected from the group consisting of A^2-NR^a-A^4, A^2-C(=O)-A^4, A^2-C(=O)O-A^4, A^4-C(=O)O-A^2, A^2-NHC(=O)-A^4, A^2-SO_2NH-A^4, and A^2-SO_2-A^4.

4. The compound of claim 1, wherein $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cycloalkyl, polycyclic cycloalkyl, alkenyl, alkyl, and aryl groups.

5. The compound of claim 1, wherein $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-alkylcyclohexyl, 2,2-dialkylcyclohexyl, 2,3-dialkylcyclohexyl, 2,4-dialkylcyclohexyl, 2,5-dialkylcyclohexyl, 2,6-dialkylcyclohexyl, 3,4-dialkylcyclohexyl, 3-alkylcyclohexyl, 4-alkylcyclohexyl, 3,3,5-trialkylcyclohexyl, cyclohexylmethyl, 2-aminocyclohexyl, 3-aminocyclohexyl, 4-aminocyclohexyl, 2,3-diaminocyclohexyl, 2,4-diaminocyclohexyl, 3,4-diaminocyclohexyl, 2,5-diaminocyclohexyl, 2,6-diaminocyclohexyl, 2,2-diaminocyclohexyl, 2-alkoxycyclohexyl, 3-alkoxycyclohexyl, 4-alkoxycyclohexyl, 2,3-dialkoxycyclohexyl, 2,4-dialkoxycyclohexyl, 3,4-dialkoxycyclohexyl, 2,5-dialkoxycyclohexyl, 2,6-dialkoxycyclohexyl, 2,2-dialkoxycyclohexyl, 2-alkylthiocyclohexyl, 3-alkylthiocyclohexyl, 4-alkylthiocyclohexyl, 2,3-dialkylthiocyclohexyl, 2,4-dialkylthiocyclohexyl, 3,4-dialkylthiocyclohexyl, 2,5-dialkylthiocyclohexyl, 2,6-dialkylthiocyclohexyl, 2,2-dialkylthiocyclohexyl, cyclopentyl, cycloheptyl, cyclohexenyl, isopropyl, n-butyl, cyclooctyl, 2-arylcyclohexyl, 2-phenylcyclohexyl, 2-arylalkylcyclohexyl, 2-benzylcyclohexyl, 4-phenylcyclohexyl, adamantyl, isocamphenyl, carenyl, 7,7-dialkylnorbornyl, bornyl, norbornyl, and decalinyl groups.

6. The compound of claim 1, wherein $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-methylcyclohexyl, 2,2-dimethylcyclohexyl, 2,3-dimethylcyclohexyl, 2,4-dimethylcyclohexyl, 2,5-dimethylcyclohexyl, 2,6-dimethylcyclohexyl, 3,4-dimethylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, cyclohexenyl, 3,3,5-trimethylcyclohexyl, 4-*t*-butylcyclohexyl, cyclohexylmethyl, isopinocampheyl, 7,7-dimethylnorbornyl, 4-isopropylcyclohexyl, and 3-methylcycloheptyl groups.

7. The compound of claim 1, wherein $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups.

8. The compound of claim 1, wherein $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups.

9. The compound of claim 1, wherein $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups.

10. The compound of claim 1, wherein $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups.

11. The compound of claim 1, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl group.

12. The compound of claim 1, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted saturated heterocyclyl group comprising at least one heteroatom selected from the group consisting of O, S, and N, in addition to the nitrogen atom to which $R^{1'}$ and $R^{2'}$ are bound.

13. The compound of claim 1, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted piperazino, morpholino, pyrrolidino, piperidino, homopiperazino, or azepino group.

14. The compound of claim 1, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazino group optionally substituted by one or two methyl groups.

15. The compound of claim 1, wherein R^a is H.

16. The compound of claim 1, wherein A^3 is a covalent bond.

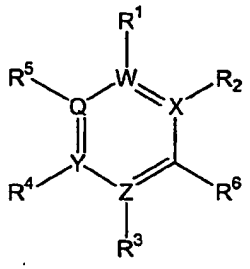
17. The compound of claim 1, wherein A^4 is a 2,4-disubstituted phenylethyl group or an indolylethyl group.

18. The compound of claim 1, wherein A^4 is selected from the group consisting of 2,4-dihalophenylethyl, and 2,4-dialkylphenylethyl groups.

19. The compound of claim 1, wherein A^4 is selected from the group consisting of phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 2-fluoro-4-bromophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-fluorophenylethyl, 2,4-

difluorophenylethyl, 2,4-dimethylphenylethyl, or 2,4-dimethoxyphenylethyl groups.

20. A compound of formula I

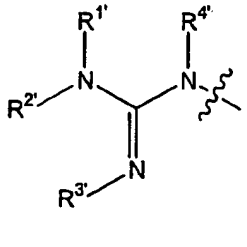


I

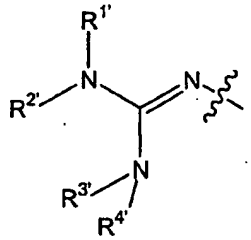
wherein

Q, W, X, Y, and Z are independently selected from the group consisting of carbon atoms and nitrogen atoms;

R^1, R^2, R^3, R^4, and R^5 may be the same or different, and are each independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted aryl, alkoxy, amino, alkyl, alkenyl, alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, heteroarylaminocarbonyl groups, and groups of formula IIA or IIB;



IIA



IIB

wherein R^1 may be absent if W is a nitrogen atom;

wherein R^2 may be absent if X is a nitrogen atom;

wherein R^3 may be absent if Z is a nitrogen atom;

wherein R^4 may be absent if Y is a nitrogen atom;

wherein R^5 may be absent if Q is a nitrogen atom;

wherein one of R^1, R^2, R^3, R^4, or R^5 is a group having the formula IIA or IIB;

$R^{1'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

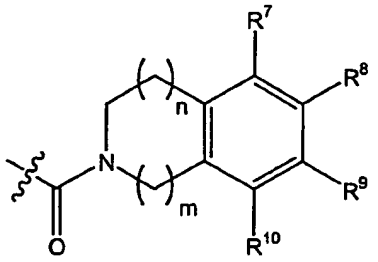
$R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

or $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl or heteroaryl group;

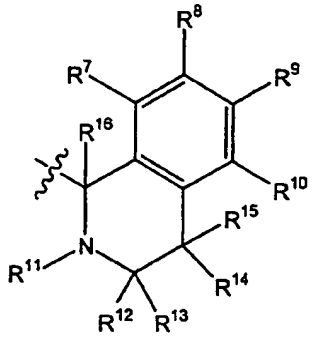
$R^{3'}$ is selected from the group consisting of substituted and unsubstituted aryl, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, arylalkyl, heteroarylalkyl, and cycloalkylalkyl groups;

$R^{4'}$ is selected from the group consisting of H, and substituted and unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, arylalkyl, and heteroarylalkyl groups;

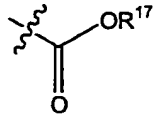
R^6 is a group of formula IIIA, IIIB, IIIC, IIID, or IIIE



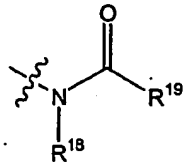
IIIA



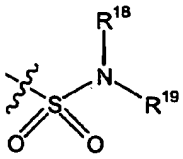
IIIB



IIIC



IIID



IIIE ;

m is an integer selected from 0, 1, or 2;

n is an integer selected from 0, 1, or 2;

R^7, R^8, R^9, and R^{10} may be the same or different and are independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted alkoxy, amino, alkyl, aryl, alkenyl, alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, and heteroarylaminocarbonyl groups;

R^7 and R^8 may join together with the carbon atoms to which they are attached to form a substituted or unsubstituted 5 or 6 membered ring;

R^{11} is selected from the group consisting of H, and substituted and unsubstitued alkyl groups;

R^{12}, R^{13}, R^{14}, and R^{15} may be the same or different and are each independently selected from the group consisting of H, Cl, I, F, Br, OH, NH_2, CN, NO_2, and substituted and unsubstituted alkoxy, amino, alkyl, aryl, alkenyl, alkynyl, alkylamino, dialkylamino, cycloalkyl, heterocyclylamino, heteroarylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, and heteroarylaminocarbonyl groups;

R^{12} and R^{14} may represent a second bond between the carbon bonded to R^{12} and the carbon bonded to R^{14} such that the bond between the carbon bonded to R^{12} and the carbon bonded to R^{14} is a double bond; and

R^{16} is selected from the group consisting of H, and substituted and unsubstituted alkyl groups;

R^{11} and R^{16} may represent a second bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} such that the bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} is a double bond;

R^{17} is selected from the group consisting of H, and substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups;

R^{18} is selected from the group consisting of H, and substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups;

R^{19} is selected from the group consisting of substituted and unsubstituted arylalkyl, heteroarylalkyl, aryl, heteroaryl, heterocyclyl,

cycloalkyl, heterocyclylalkyl, cycloalkylalkyl, alkenyl, alkynyl, and alkyl groups; and

prodrugs thereof, pharmaceutically acceptable salts thereof, stereoisomers thereof, tautomers thereof, hydrates thereof, hydrides thereof, or solvates thereof.

21. The compound of claim 20, wherein R^6 has the formula IIIA.

22. The compound of claim 21, wherein m is 0 and n is 2.

23. The compound of claim 21, wherein m is 1 and n is 1.

24. The compound of claim 21, wherein m is 0 and n is 1.

25. The compound of claim 21, wherein m is 2 and n is 1.

26. The compound of claim 20, wherein R^6 has the formula IIIB.

27. The compound of claim 26, wherein R^{11} and R^{16} represent a second bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} such that the bond between the carbon bonded to R^{16} and the nitrogen bonded to R^{11} is a double bond.

28. The compound of claim 26, wherein R^{11} is H or a substituted or unsubstituted alkyl group and R^{16} is H.

29. The compound of claim 26, wherein at least one of R^8 or R^9 is selected from the group consisting of Br, Cl, F, I, substituted and unsubstituted alkyl groups, and substituted and unsubstituted alkoxy groups.

30. The compound of claim 20, wherein R^6 has the formula IIIC.

31. The compound of claim 20, wherein R^6 has the formula IIID.

32. The compound of claim 20, wherein R^6 has the formula IIIE.

33. The compound of claim 20, wherein R^6 has the formula IIID or IIIE and R^{18} is H.

34. The compound of claim 20, wherein R^6 has the formula IIIC, IIID, or IIIE wherein R^{17} or R^{19} is selected from the group consisting of substituted and unsubstituted arylalkyl groups, and substituted and unsubstituted heteroarylalkyl groups.

35. The compound of claim 34, wherein R^{17} or R^{19} is a substituted or unsubstituted phenylalkyl group or a substituted or unsubstituted indolylalkyl group:

36. The compound of claim 34, wherein R^{17} or R^{19} is a 2,4-disubstituted phenylethyl group or an indolylethyl group.

37. The compound of claim 34, wherein R^{17} or R^{19} is selected from the group consisting of 2,4-dihalophenylethyl, and 2,4-dialkylphenylethyl groups.

38. The compound of claim 34, wherein R^{17} or R^{19} is selected from the group consisting of phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-chlorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolylethyl, 4-hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-fluoro-4-methylphenylethyl, 2-fluoro-4-bromophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-fluorophenylethyl, 2,4-

difluorophenylethyl, 2,4-dimethylphenylethyl, or 2,4-dimethoxyphenylethyl groups.

39. The compound of claim 31, wherein R^{19} is a substituted arylalkyl group, and the alkyl group of the R^{19} arylalkyl group is substituted with an amino or acetamido group.

40. The compound of claim 20, wherein Q is a carbon atom and R^5 has the formula IIA or IIB.

41. The compound of claim 20, wherein Q, W, X, Y, and Z are all carbon atoms.

42. The compound of claim 20, wherein one of Q, W, X, Y, or Z is a nitrogen atom.

43. The compound of claim 20, wherein $R^{4'}$ is an H.

44. The compound of claim 20, wherein $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cycloalkyl, polycyclic cycloalkyl, alkenyl, alkyl, and aryl groups.

45. The compound of claim 20, wherein $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-alkylcyclohexyl, 2,2-dialkylcyclohexyl, 2,3-dialkylcyclohexyl, 2,4-dialkylcyclohexyl, 2,5-dialkylcyclohexyl, 2,6-dialkylcyclohexyl, 3,4-dialkylcyclohexyl, 3-alkylcyclohexyl, 4-alkylcyclohexyl, 3,3,5-trialkylcyclohexyl, cyclohexylmethyl, 2-aminocyclohexyl, 3-aminocyclohexyl, 4-aminocyclohexyl, 2,3-diaminocyclohexyl, 2,4-diaminocyclohexyl, 3,4-diaminocyclohexyl, 2,5-diaminocyclohexyl, 2,6-diaminocyclohexyl, 2,2-diaminocyclohexyl, 2-alkoxycyclohexyl, 3-alkoxycyclohexyl, 4-alkoxycyclohexyl, 2,3-dialkoxycyclohexyl, 2,4-dialkoxycyclohexyl, 3,4-dialkoxycyclohexyl, 2,5-dialkoxycyclohexyl, 2,6-dialkoxycyclohexyl, 2,2-dialkoxycyclohexyl, 2-alkylthiocyclohexyl, 3-alkylthiocyclohexyl, 4-alkylthiocyclohexyl, 2,3-dialkylthiocyclohexyl, 2,4-dialkylthiocyclohexyl, 3,4-dialkylthiocyclohexyl, 2,5-

dialkylthiocyclohexyl, 2,6-dialkylthiocyclohexyl, 2,2-dialkylthiocyclohexyl, cyclopentyl, cycloheptyl, cyclohexenyl, isopropyl, n-butyl, cyclooctyl, 2-arylcyclohexyl, 2-phenylcyclohexyl, 2-arylalkylcyclohexyl, 2-benzylcyclohexyl, 4-phenylcyclohexyl, adamantyl, isocamphenyl, carenyl, 7,7-dialkylnorbornyl, bornyl, norbornyl, and decalinyl groups.

46. The compound of of claim 20, wherein $R^{3'}$ is selected from the group consisting of substituted and unsubstituted cyclohexyl, 2-methylcyclohexyl, 2,2-dimethylcyclohexyl, 2,3-dimethylcyclohexyl, 2,4-dimethylcyclohexyl, 2,5-dimethylcyclohexyl, 2,6-dimethylcyclohexyl, 3,4-dimethylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, cyclohexenyl, 3,3,5-trimethylcyclohexyl, 4-*t*-butylcyclohexyl, cyclohexylmethyl, isopinocampheyl, 7,7-dimethylnorbornyl, 4-isopropylcyclohexyl, and 3-methylcycloheptyl groups.

47. The compound of claim 20, wherein $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups.

48. The compound of claim 20, wherein $R^{1'}$ is H and $R^{2'}$ is selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups.

49. The compound of claim 20, wherein $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted alkyl, arylalkyl, and heteroarylalkyl groups.

50. The compound of claim 20, wherein $R^{1'}$ and $R^{2'}$ may be the same or different and are each independently selected from the group consisting of substituted and unsubstituted dialkylaminoethyl, 4-ethylbenzyl,

3-chlorobenzyl, 2,4-dichlorobenzyl, 3-methylbenzyl, benzyl, 4-fluorobenzyl, 3-methoxybenzyl, 2-chlorobenzyl, and thiophene groups.

51. The compound of claim 20, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted heterocyclyl group.

52. The compound of claim 51, wherein R^{17} is H or an unsubstituted alkyl group.

53. The compound of claim 52, wherein $R^{3'}$ is a substituted cycloalkyl group or a substituted polycyclic cycloalkyl group.

54. The compound of claim 20, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted saturated heterocyclyl group comprising at least one heteroatom selected from the group consisting of O, S, and N, in addition to the nitrogen atom to which $R^{1'}$ and $R^{2'}$ are bound.

55. The compound of claim 54, wherein R^{17} is H or an unsubstituted alkyl group.

56. The compound of claim 20, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a substituted or unsubstituted piperazino, morpholino, pyrrolidino, piperidino, homopiperazino, or azepino group.

57. The compound of claim 56, wherein R^{17} is H or an unsubstituted alkyl group.

58. The compound of claim 20, wherein $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound, form a piperazino group optionally substituted by one or two methyl groups.

59. A composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

60. A composition comprising the compound according to claim 20 and a pharmaceutically acceptable carrier.

61. A method of treating an MC4-R mediated disease, comprising administering to a subject in need thereof, the compound according to claim 1.

62. The method according to claim 61, wherein the disease is obesity or type II diabetes.

63. A method of treating an MC4-R mediated disease, comprising administering to a subject in need thereof, the compound according to claim 20.

64. The method according to claim 63, wherein the disease is obesity or type II diabetes.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 August 2003 (14.08.2003)

PCT

(10) International Publication Number
WO 2003/066597 A3

(51) International Patent Classification[7]: C07D 215/08, 217/06, 209/08, 223/16, 217/14, 221/10, 401/04, 401/06, 295/12, 295/20, A61K 31/47, 31/4709, 31/472, 31/4725, 31/495, 31/496, A61P 3/04, 3/10

(21) International Application Number:
PCT/US2003/001078

(22) International Filing Date: 3 February 2003 (03.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/353,188	4 February 2002 (04.02.2002)	US
10/351,574	27 January 2003 (27.01.2003)	US

(71) Applicant *(for all designated States except US)*: **CHIRON CORPORATION** [US/US]; 4560 Horton Street, Emeryville, CA 94608 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BOYCE, Rustum** [IN/US]; 1818 Broadway #206, San Francisco, CA 94109 (US). **CHU, Daniel** [US/US]; 3767 Benton Street, Santa Clara, CA 95051 (US).

(74) Agents: COLLIER, Steven, W. et al.; Chiron Corporation, Intellectual Property R338, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
1 April 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/066597 A3

(54) Title: GUANIDINO COMPOUNDS

(57) Abstract: A variety of small, guanidino group-containing molecules capable of acting as MC4-R agonists are provided. The compounds have various structures provided herein. The compounds are useful in treating MC4-R mediated diseases and may be formulated into pharmaceutical formulations and compositions.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/01078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/08 C07D217/06 C07D209/08 C07D223/16 C07D217/14
C07D221/10 C07D401/04 C07D401/06 C07D295/12 C07D295/20
A61K31/47 A61K31/4709 A61K31/472 A61K31/4725 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 343 894 A (PFIZER) 29 November 1989 (1989-11-29) cited in the application claims 1,9,10 & US 4 948 901 A 14 August 1990 (1990-08-14) cited in the application & US 4 874 864 A cited in the application ---	1,20,59, 60
A	US 4 732 916 A (MATSUMOTO HITOSHI ET AL) 22 March 1988 (1988-03-22) cited in the application claims ---	1,20,59, 60

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2003	20/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/01078

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/496 A61P3/04 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 352 704 A (OKUYAMA AKIRA ET AL) 4 October 1994 (1994-10-04) cited in the application claims; examples	1,20,59, 60
A	US 4 211 867 A (RASMUSSEN CHRIS R) 8 July 1980 (1980-07-08) cited in the application column 16, line 15 -column 19 column 41 -column 84 abstract; claim 1	1,20,59, 60
A	US 5 952 381 A (RICO JOSEPH G ET AL) 14 September 1999 (1999-09-14) cited in the application claims 1,7; examples	1,20,59, 60

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/01078

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 55107 A (PETT CHRISTOPHER PHINEAS; KAULINA LARISA (LV); KREICBERGA JANA (LV) 2 August 2001 (2001-08-02) cited in the application abstract; claims 1,9,11,12,14-46	1,20, 59-64
A	WO 00 58361 A (PROCTER & GAMBLE) 5 October 2000 (2000-10-05) abstract page 17 page 24 -page 27 claims 1,11-15	1,20, 59-64
A	WO 00 35952 A (PETT CHRISTOPHER PHINEAS; MUTULE ILZE (SE); MUCENIECE RUTA (SE); M) 22 June 2000 (2000-06-22) claims 1,20-30	1,20, 59-64
A	WO 01 10842 A (DAI MINGSHI; VOS TRICIA J (US); MAGUIRE MARTIN P (US); MILLENNIUM) 15 February 2001 (2001-02-15) cited in the application claims	1,20, 59-64
P,X	WO 02 081443 A (CHANG BRYAN; CHIRON CORP (US); BOYCE RUSTUM S (US); CHU DANIEL (US) 17 October 2002 (2002-10-17) claims	1,59-64
A,P	WO 02 18327 A (CHIRON CORP; MYLES DAVID (US); TOZZO EFFIE (US); BOYCE RUSTUM (US)) 7 March 2002 (2002-03-07) claims	1,59-64

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/01078

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 61-64 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 2, 4-13, 17, 20, 28, 29, 34-36, 39, 44-51, 53, 54, 56 (all partly)

The scope of the group of compounds defined by the functional term "prodrugs" is unclear within the meaning of Article 6 PCT, as it is not possible to assign a molecular structure to this group.

The scope of the group of compounds defined by the term "hydrides" is uncler within the meaning of Article 6 PCT, as is is not ready comprehensible where a hydride function shall be present in the molecules.

Moreover, the term "substituted" or "disubstituted", used several times in the claims without any proper definition which concrete substituents shall be comprised, is not clear as to the very scope of the subject-matter for which protection is sought (Art. 6 PCT).

Therefore it was not possible to carry out a complete search over the whole scope claimed. Consequently, the parts of the claims referring to "prodrugs", to "hydrides" and to "substituted", i.e. optional substituents without any concrete definition, have not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[illegible] Application No
PCT/US 03/01078

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0343894	A	29-11-1989	US	4874864 A	17-10-1989
			AT	77083 T	15-06-1992
			AU	602294 B2	04-10-1990
			AU	3509789 A	30-11-1989
			DE	68901746 D1	16-07-1992
			DE	68901746 T2	17-12-1992
			DK	249089 A	27-11-1989
			EP	0343894 A1	29-11-1989
			ES	2032229 T3	16-01-1993
			FI	892497 A ,B,	25-11-1989
			GR	3005072 T3	24-05-1993
			HU	49860 A2	28-11-1989
			HU	201314 B	28-10-1990
			IE	61151 B1	05-10-1994
			IL	90336 A	31-01-1993
			JP	1939388 C	09-06-1995
			JP	2017177 A	22-01-1990
			JP	6067905 B	31-08-1994
			KR	9104207 B1	24-06-1991
			NO	892058 A ,B,	27-11-1989
			NZ	229235 A	26-06-1990
			PT	90623 A ,B	30-11-1989
			US	4948891 A	14-08-1990
			US	4948901 A	14-08-1990
			ZA	8903865 A	30-01-1991
US 4732916	A	22-03-1988	JP	62029566 A	07-02-1987
			AT	46501 T	15-10-1989
			DE	3665711 D1	26-10-1989
			EP	0218027 A1	15-04-1987
			ES	2001341 A6	16-05-1988
			PT	83104 A ,B	01-08-1986
US 5352704	A	04-10-1994	CA	2032420 A1	23-06-1991
			DE	69008682 D1	09-06-1994
			EP	0434432 A1	26-06-1991
			JP	3236366 A	22-10-1991
US 4211867	A	08-07-1980	AT	356669 B	12-05-1980
			AT	190677 A	15-10-1979
			AU	517804 B2	27-08-1981
			AU	2335177 A	21-09-1978
			BE	852565 A1	19-09-1977
			CA	1100494 A1	05-05-1981
			CH	632994 A5	15-11-1982
			CH	634557 A5	15-02-1983
			CH	636084 A5	13-05-1983
			CH	635073 A5	15-03-1983
			CS	225804 B2	13-02-1984
			DD	130242 A5	15-03-1978
			DE	2711757 A1	22-09-1977
			DK	119477 A	20-09-1977
			ES	457010 A1	16-07-1978
			FI	770864 A ,B,	20-09-1977
			FR	2361366 A1	10-03-1978
			GB	1573532 A	28-08-1980
			GR	60780 A1	28-08-1978
			IE	44792 B1	07-04-1982

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[illegible] Application No
PCT/US 03/01078

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4211867 A		IL 51694 A	31-01-1982
		JP 52136168 A	14-11-1977
		JP 63027342 B	02-06-1988
		NL 7703011 A	21-09-1977
		NO 770959 A ,B,	20-09-1977
		NZ 183570 A	08-06-1979
		PH 16561 A	18-11-1983
		PL 110453 B1	31-07-1980
		RO 71209 A1	04-11-1981
		SE 423628 B	17-05-1982
		SE 7703114 A	20-09-1977
		SU 795471 A3	07-01-1981
		ZA 7701644 A	25-10-1978
US 5952381 A	14-09-1999	US 6251944 B1	26-06-2001
		AT 212978 T	15-02-2002
		AU 2536097 A	22-10-1997
		CA 2250698 A1	09-10-1997
		DE 69710319 D1	21-03-2002
		DE 69710319 T2	14-08-2002
		DK 891325 T3	21-05-2002
		EP 1157985 A1	28-11-2001
		EP 0891325 A1	20-01-1999
		ES 2172780 T3	01-10-2002
		JP 2000515493 T	21-11-2000
		PT 891325 T	31-07-2002
		WO 9736859 A1	09-10-1997
WO 0155107 A	02-08-2001	AU 2868101 A	07-08-2001
		WO 0155107 A2	02-08-2001
WO 0058361 A	05-10-2000	AU 763510 B2	24-07-2003
		AU 4017900 A	16-10-2000
		BR 0009497 A	15-01-2002
		CA 2368431 A1	05-10-2000
		CN 1345335 T	17-04-2002
		CZ 20013407 A3	13-02-2002
		EP 1165613 A1	02-01-2002
		HU 0202203 A2	28-10-2002
		JP 2002542159 T	10-12-2002
		NO 20014568 A	29-11-2001
		NZ 514141 A	28-09-2001
		PL 350095 A1	04-11-2002
		SK 13082001 A3	05-03-2002
		TR 200102765 T2	21-05-2002
		WO 0058361 A1	05-10-2000
		US 6613874 B1	02-09-2003
		ZA 200107411 A	12-03-2002
WO 0035952 A	22-06-2000	AU 1789900 A	03-07-2000
		WO 0035952 A2	22-06-2000
WO 0110842 A	15-02-2001	AU 6621600 A	05-03-2001
		BR 0012984 A	16-07-2002
		CA 2381008 A1	15-02-2001
		EP 1204645 A2	15-05-2002
		WO 0110842 A2	15-02-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/01078

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02081443 A	17-10-2002	WO 02081443 A1	17-10-2002
		US 2002193595 A1	19-12-2002
WO 0218327 A	07-03-2002	AU 8860401 A	13-03-2002
		CA 2420694 A1	07-03-2002
		CZ 20030882 A3	17-09-2003
		HU 0302067 A2	29-09-2003
		NO 20030929 A	30-04-2003
		WO 0218327 A2	07-03-2002
		US 2002137939 A1	26-09-2002